Volume 7 **Neurology** *Number 10*

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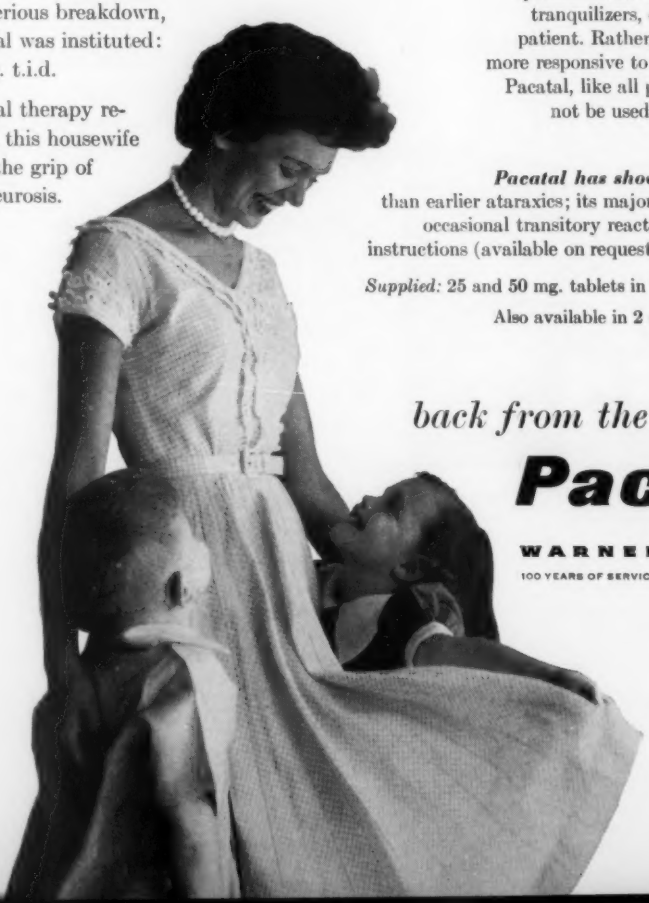

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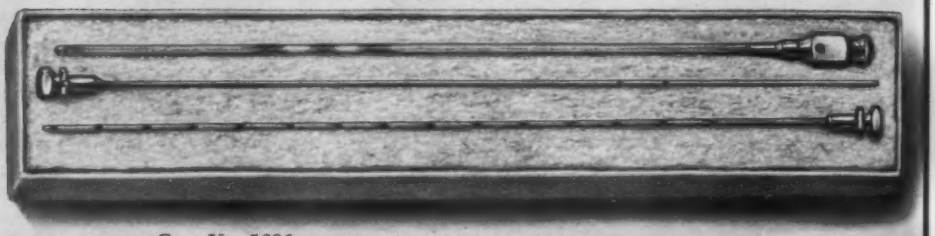

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*Cooper, I. S.: Chemopallidectomy: An Investigation Technique in Geriatric Parkinsonians, Science 121: 217-218 Feb. 1955.

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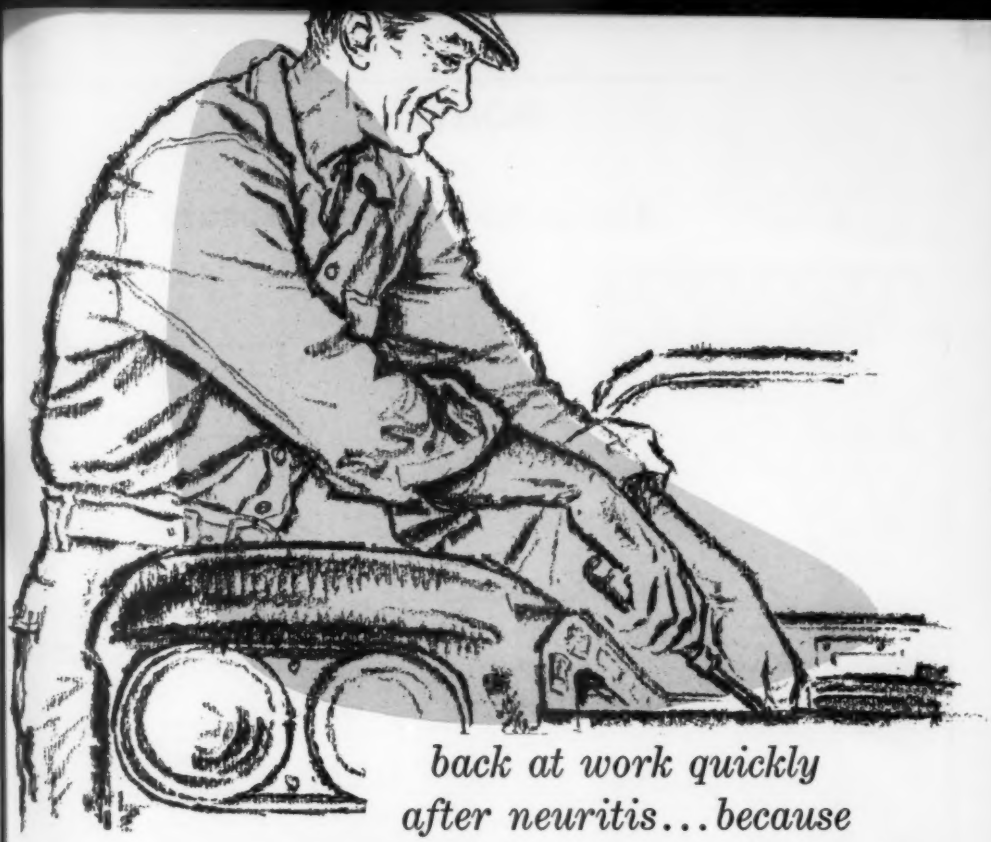

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1. Smith, R. T.: M. Clin. North America, March 1957. 2. Smith, R. T.: New York Med. 5:16, 1952.
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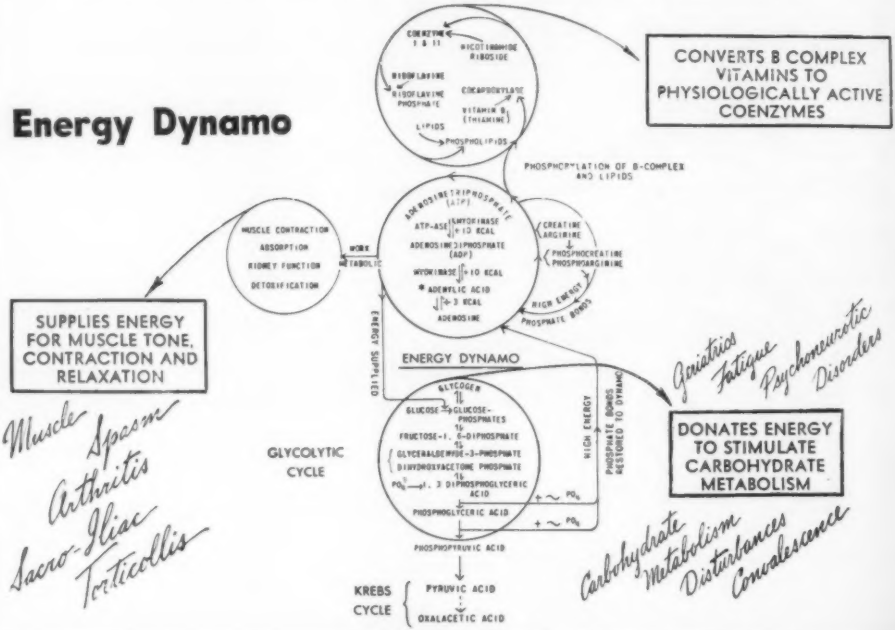

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CLINICAL EXPERIENCE: Data in over 600 of the hundreds of patients treated with Vesprin to date have been carefully analyzed.

In 1 series of 55 hospitalized psychotic patients treated with Vesprin, marked to moderate improvement occurred in approximately 66 per cent.

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In a third series of 123 psychotic patients treated with Vesprin for more than 3 months, 5 recovered from all of their active psychotic manifestations, particularly delusions and hallucinations, and 24 recovered from most psychotic manifestations with good social remission. An additional 78 patients showed significant improvement in their psychotic behavior.

Another group of schizophrenic patients has been treated with Vesprin for periods ranging from 6 months to 1 year. During this time clinical laboratory studies were made weekly, and later monthly, on urine and blood of the patients.

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- **Hyperthermia...rare**
- **Convulsions...not observed**

studies gave no evidence of drug toxicity.
Another investigator thought that Vesprin appeared to be more active and rapid in effect. The best response to Vesprin was seen in overactive, troublesome schizophrenic patients.

WHAT ARE THE ADVANTAGES? Clinical experience in hundreds of patients has shown that Vesprin does not oversedate the patient into sleepiness, drowsiness and lethargy. Drug-induced agitation is minimal.
Vesprin is active and rapid in controlling manic states, excitement and panic, and also in controlling the disturbing effects of delusions and hallucinations. Vesprin moderates hostile behavior and facilitates insight.
With Vesprin, intractable behavior patterns are rapidly brought under control. Thus, patients are made accessible to psychotherapy. Nursing care is reduced, and the patients' social rehabilitation is facilitated.
Extensive clinical experience has shown Vesprin to be singularly free from toxicity. Clinicians who have worked with the drug over long periods have not seen jaundice or liver damage, blood dyscrasias, or convulsions. Skin eruptions, photosensitivity or hyperthermia have been rarely observed.

WHAT ARE THE SIDE EFFECTS? Investigators have reported such symptoms as dizziness, nausea, weakness, drowsiness and epigastric distress in patients treated with Vesprin. Postural hypotension has been seen occasionally in normotensive patients. A hypotensive effect has been observed in patients with high blood pressure.
Anxiety and restlessness have been observed in some patients, and gain in weight in a few. These effects have usually been mild, and, as a rule have disappeared when the dosage was reduced or treatment stopped.
The most commonly encountered side effect has been the development of a Parkinson-like syndrome with motor disturbances and extrapyramidal symptoms. This syndrome is reversible and symptoms usually subside with a reduction of dosage or discontinuance of medication for 2 or 3 days.

VESPRIN

Squibb Triflupromazine

WHEN IS IT INDICATED? Vesprin is indicated in treatment of various acute and chronic psychoses. Because it ameliorates psychomotor hyperactivity and assaultive behavior, Vesprin is particularly useful in management of schizophrenia, manic states, sociopathic personality disturbances with psychotic reactions, mental deficiency with psychoses, and psychoses associated with organic brain disease and senility.
Contraindications: Vesprin is contraindicated in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates).

WHAT IS THE DOSAGE? The recommended adult dosage of Vesprin is 25 mg. t.i.d., to be adjusted according to patient response. This dose may be increased until the desired clinical effect has been achieved, or until unwanted side effects become a problem.
The initial dose for children is 10 mg. t.i.d.
The suggested starting dose in geriatric patients is 10 mg. t.i.d. The dosage in children and elderly patients may be increased according to patient response.
The optimum dose of Vesprin varies from patient to patient and should be established on an individual basis. In the majority of patients, prolonged treatment is required for maximum clinical response.
Caution: Although no deleterious effects on the hemopoietic system have occurred to date in the extensive clinical use of Vesprin, routine blood counts are suggested during the course of therapy.
Patients should be watched for indications of soreness of the mouth, gums or throat, or for symptoms of upper respiratory infection. If these complications occur, and a confirmatory leukocyte count indicates cellular depression, the agent should be stopped and appropriate treatment, including intensive antibiotic therapy, should be started immediately.

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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Neurology Volume 7 • Number 10

Significance of Symptoms and Signs in Localization of Involved Root in Cervical Disk Protrusion

Robert E. Yoss, M.D., Kendall B. Corbin, M.D., Collin S. MacCarty, M.D. and J. Grafton Love, M.D.

NEUROLOGIC SYMPTOMS and signs due to cervical root compression vary, not only when roots at different levels are involved but also when roots at the same level are affected. An effort has been made to determine the reliability of various symptoms and signs in determining the level of compression when a single cervical root is compressed by a protruded cervical disk. To be of value, such a study must deal with a significantly large group of patients, with reliable evidence indicating the exact nerve root which is compressed and with an adequate anamnesis and examination.

MATERIAL AND METHODS

The selection of cases was based on the following criteria: 1) surgically verified nerve-root compression due to protrusion of a cervical disk; 2) sufficient information to support the surgeon's impression as to the specific root involved, that is, roentgenologic evidence from the placement of a silver clip at the involved interspace at the time of removal of the disk, or myelographic evidence of protrusion of a single cervical disk limited to one interspace or both; and 3) relief of symptoms, especially pain, after decompression of a single cervical root. Decompression of a root should result in relief of symptoms if the symptoms are due to involvement of that particular root rather than to compression of another root by an unrecognized lesion. All cases were excluded from this study if the history, neurologic examination, and surgical note were not sufficiently clear or complete. In addition, cases in which multiple or bilateral root compression or spinal cord compression was present were excluded.

The first 100 cases that satisfied the established criteria were selected from the files of the Mayo Clinic; all were encountered within a six-year period extending from March 1950 through February 1956. The histories, neurologic examinations, and surgical procedures had been carried out by members of the sections of neurology and of neurologic surgery.

GENERAL DATA

The single roots involved in this study were limited to the fifth, sixth, seventh, and eighth cervical roots (roots C-5, C-6, C-7, and C-8) which had been compressed by protrusions of cervical disks between the appropriate adjacent vertebrae. In 69 of the 100 cases the root compressed was C-7. Root C-5 was compressed in 2 per cent, C-6 in 19 per cent, and C-8 in 10 per cent. We have not attempted, in this study, to collect data regarding multiple root compressions or to analyze presumed protrusions of cervical disks in patients who had not undergone surgical procedures. Men outnumbered women in the ratio of four to one. The left side was involved in 61 per cent of our group. The ages of the patients at the time of operation ranged from 30 to 65 years, with a median age of 46 years.

In 79 patients silver clips had been placed during surgical procedures to mark the site of the root decompression. In each case the site was confirmed postoperatively by roentgenologic examination. Of this group, 30 patients also had myelographic confirmation of the level

From the sections of neurology and neurologic surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 25, 1957.

involved. Although we believe that a metal clip placed by the surgeon is the most reliable method of confirming the level of the root involved, 21 patients of this series had preoperative myelographic confirmation only. In each instance, the findings were interpreted by the radiologist and the neurosurgeon as showing a single defect from a protruded cervical disk. Those cases in which myelographic examination alone was not definite for a single protruded disk were excluded from our series. This method of identification of the compressed root was essential. Surgical verification alone is not sufficient in an analysis of this type, since specific localization of the compressed root during operation may be difficult.

Examinations of spinal fluid were done preoperatively in 93 of our 100 patients. None of the patients showed evidence of subarachnoid block. Thirty-seven of them had a value for total protein in the cerebrospinal fluid exceeding 45 mg. per 100 cc., which is considered to be the upper limit of normal in our laboratory (figure 1).

SYMPTOMS

Pain in Neck and Shoulders. Pain in the neck was recorded in 56 patients. It should be noted that this is the minimal incidence, since in some patients the pain may have been minor or may have occurred in the distant past and, therefore, was not mentioned. Fifteen of the 21 patients (71 per cent) with involvement of root C-5 or C-6 complained of such pain; 41 of the 79 patients (52 per cent) with compression of root C-7 or C-8 complained of this symptom. Interscapular or scapular pain was reported by 37 patients: 31 of the 79 patients (39 per cent) who had involvement of root C-7 or C-8, and six of the 21 patients (29 per cent) who had involvement of root C-5 or C-6. Pain in the shoulder was recorded in 78 patients (table 1).

Pain in the Arm. Pain was present in the arm (upper) in 99 patients, but it was poorly localized or at least poorly described in 52. Of the remaining 47 patients seven localized their pain to the medial aspect of the arm, 25 to the lateral, one to the anterior, and 14 to the posterior aspects. Pain localized to the lateral aspect of the arm was associated with compression of roots C-5, C-6, C-7, and C-8, but the incidence was higher for roots C-5, C-6, and C-7 than for root C-8 (table 1). Pain located in the posterior aspect of the arm, whether posterolateral or posteromedial, occurred in 14 cases, 11 of which had compression of root C-7. Pain in the medial aspect of the arm occurred in seven cases and was due to compression of either root C-7 (three cases) or root C-8 (four cases).

Pain in the Forearm. Pain in the forearm occurred in 88 per cent of this group. Some of these patients mentioned paresthesia in the same areas as the pain. In contrast, however, paresthesia was not mentioned specifically along with pain in the neck, interscapular or scapular regions, shoulder, or arm. Only 38 of the 88 patients were able to localize pain to specific portions of the forearm (table 2). Radial pain was limited to compression of root C-6 or C-7. Neither of the patients who had compression of root C-5 had pain or paresthesia below the elbow. Ulnar pain in six of the nine patients who experienced it was due to involvement of root C-8; in the other three patients root C-7 was compressed. Twelve of the 13 patients with pain localized on the dorsal or volar surface of the forearm had compression of root C-7.

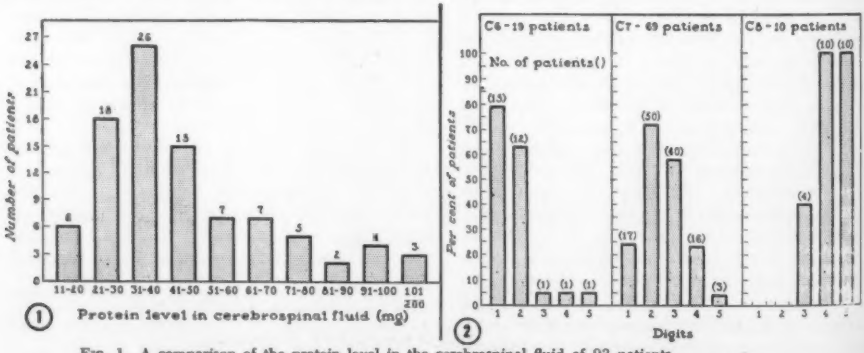

Number of patients
11-20 21-30 31-40 41-50 51-60 61-70 71-80 81-90 91-100 101 200
Protein level in cerebrospinal fluid (mg)
C6 - 19 patients
C7 - 69 patients
C8 - 10 patients
No. of patients()
Per cent of patients
Digits

FIG. 1. A comparison of the protein level in the cerebrospinal fluid of 93 patients.
FIG. 2. Incidence of paresthesia in the digits due to compression of roots C-6, C-7, and C-8.

TABLE 1
INCIDENCE OF PAIN IN NECK, SCAPULAR OR INTERSCAPULAR REGION, SHOULDER, OR ARM

Location and incidence of pain	*Root compressed* C-5 (2 patients)	C-6 (19 patients)	C-7 (69 patients)	C-8 (10 patients)	*Total cases*
Neck					
Number	2	13	38	3	56
Per cent	100	68	55	30	
Scapular or interscapular region					
Number	0	6	26	5	37
Per cent	–	32	38	50	
Shoulder					
Number	2	13	57	6	78
Per cent	100	68	83	60	
Arm (localized)	2	5	32	8	47
Anterior aspect					
Number	0	0	1	0	1
Per cent	–	–	3	0	
Lateral aspect					
Number	2	4	17	2	25
Per cent	100	80	53	25	
Posterior aspect					
Number	0	1	11	2	14
Per cent	–	20	34	25	
Medial aspect					
Number	0	0	3	4	7
Per cent	–	–	9	50	

Paresthesia. Paresthesia in the hand, with or without pain, occurred in 91 per cent of the 100 patients.

The thumb and index finger were most frequently involved when root C-6 was compressed (figure 2). Involvement of root C-7 caused sensory disturbances in the index and middle fingers and also occasionally in the thumb and ring finger. Compression of root C-8 limited involvement to digits 3, 4, and 5, with major effects in the ring and little fingers.

Paresthesia with or without pain and limited to the thumb occurred in four patients, all of whom had compression of nerve root C-6 (figure 3). Pain or paresthesia of the thumb and index finger was the commonest pattern of sensory involvement; in 11 patients it was caused by involvement of root C-6 and in seven patients by compression of root C-7 (figure 3). Paresthesia limited to the thumb, index, and middle fingers occurred in ten patients and was always due to compression of root C-7, as was paresthesia of the index finger alone in seven of the eight patients in whom it occurred. The second commonest digital pattern in our 100 patients involved the index and middle fingers and occurred in 15 patients; in all 15 cases, irritation of root C-7 was the cause. Similarly, paresthesia in the index, middle, and ring fingers present in 11 patients and of the middle and ring fingers in two patients was due to involvement of root C-7. Involvement of the three ulnar digits occurred in seven patients; in four, nerve root C-8 was compressed, in two, root C-7, and in one, root C-6. The ring and little fingers were involved in seven patients, in six of whom root C-8 was involved. Nine patients mentioned paresthesia with or without pain in the fingers, but they were not sure which digit was involved or they felt that all the fingers were involved; the seventh cervical root of each of these patients was involved. Nine of the 100 patients denied digital paresthesia; in these patients the following nerve roots were compressed: C-5 in two patients, C-6 in two patients, and C-7 in five patients.

Muscle Weakness. Subjective weakness of the upper extremity was present in 34 cases, but 75 of the 100 patients had some objective weakness. Both patients with involvement of root C-5 complained of weakness in the shoulder. Five of the eight patients with subjective weakness due to lesions of root C-6 complained of weakness in the upper part of the arm. Subjective weakness due to involvement of root C-7 was diffuse and was not localized to any specific portion of the involved upper extremity in 14 of the 18 cases All six patients in whom root C-8 was involved and who had subjective weakness localized it to the hand.

OBJECTIVE FINDINGS

Reflexes. Triceps, biceps, and brachioradialis reflexes were checked routinely in all cases. Diminution of one or more of these three reflexes was present in 72 per cent of the cases. Three patients (one with root C-5, one with root C-6, and one with root C-7 compressed) had slight diminution of all reflexes in the involved extremity. The finding of a diminished triceps reflex was the commonest change; it

TABLE 2
PAIN OR PARESTHESIA OR BOTH LOCALIZED IN FOREARM

Root compressed	Number of patients	Location							
		Radial		Ulnar		Dorsal		Volar	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
C-5	0	0	–	0	–	0	–	0	–
C-6	7	7	100	0	–	0	–	0	–
C-7	24	9	38	3	12	9	38	3	12
C-8	7	0	–	6	86	1	14	0	–
Total	38	16		9		10		3	

was present in 51 per cent of the entire group and was limited to those patients with involvement of either root C-7 or C-8 (table 3). This represented 65 per cent of the cases in which root C-7 was compressed and 60 per cent in which C-8 was compressed. A diminished triceps reflex, with diminution of either the biceps or the brachioradialis reflex, occurred in five cases, all of which were due to involvement of root C-7. The biceps reflex alone was diminished in one instance of involvement of root C-6 and one of root C-7; the brachioradialis reflex was diminished in three cases of involvement of root C-6, and diminution of combined biceps and brachioradialis reflexes was present in one case in which root C-5, six cases in which root C-6, and one case in which root C-7 were involved.

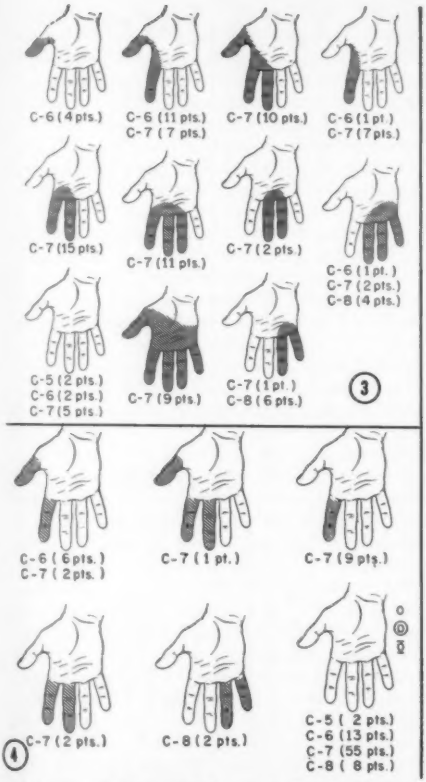
Muscle Strength. Objective weakness was recorded in 75 per cent of the series and was limited to one muscle or to several muscles. Since examinations of muscles were carried out by a number of examiners, it was sometimes difficult to determine the significance of slight or equivocal muscle weakness. Because of this, only those cases in which the weakness was definitely evident were used for this survey.

Both patients with involvement of root C-5 showed weakness in the supraspinatus, infraspinatus, and deltoid muscles and also, to a lesser extent, in the biceps and brachioradialis muscles (table 4). Thirteen of the 19 patients with involvement of root C-6 had some muscle weakness; the greatest loss of strength occurred in the biceps, brachioradialis, and wrist extensor group, with less frequent involvement in the triceps, finger flexors, and deltoid (table 4). In 69 patients with involvement of the seventh root, 65 per cent showed some weakness of the triceps, frequently the only weak muscle; the wrist extensors were also involved commonly in this group (table 4). Eight of the ten patients with compression of root C-8 showed weakness limited primarily to the intrinsic muscles of the hand and the extrinsic flexors and extensors of the digits (table 4). Other groups of muscles were tested but weakness, if present, was so slight as to be of no localizing value in this study. Figure 5 shows the relative involvement of muscles, both as to incidence and severity of weakness, with involvement of various cervical roots.

Sensory Examination. Objective sensory loss in the involved upper extremity was found in 24 patients of this series. No sensory loss was found in the region of the neck, scapula, or shoulder. One patient, whose fifth cervical root was compressed, showed a sensory deficit in the arm and one with compression of root C-7 showed a deficit in the forearm. Twenty-three patients (six with involvement of root C-6, 14 of root C-7, and three of root C-8) had some objective sensory diminution in the digits of the hand (figure 4). Six patients with involvement of root C-6 had objective sensory changes, all of which were limited to the thumb and index finger. Two of the 14 patients with objective sensory changes and lesions of root C-7 showed sensory changes in the thumb and index finger; one had hypesthesia of the thumb and index and middle fingers, nine had findings in the index finger alone, and in two patients the index and middle fingers were involved. Only three patients with in-

TABLE 3
DIMINISHED STRETCH REFLEXES IN UPPER EXTREMITIES

Root compressed	Total cases	Reflex											
		Biceps		Brachioradialis		Triceps		Biceps and Brachioradialis		Triceps and Brachioradialis		Triceps and Biceps	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
C-5	2	0	–	0	–	0	–	1	50	0	–	0	–
C-6	19	1	5	3	16	0	–	6	32	0	–	0	–
C-7	69	1	1	0	–	45	65	1	1	4	6	1	1
C-8	10	0	–	0	–	6	60	0	–	0	–	0	–
Total	100	2		3		51		8		4		1	



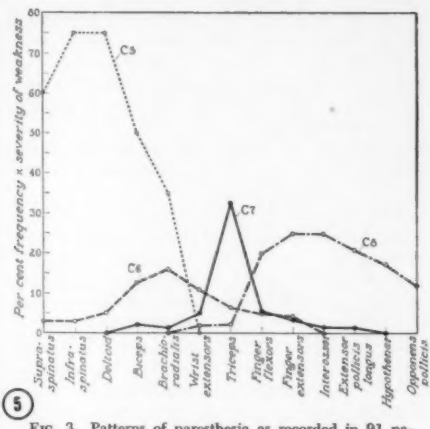


FIG. 3. Patterns of paresthesia as recorded in 91 patients.

FIG. 4. Objective sensory diminution in the digits of 23 patients.

FIG. 5. Incidence and severity of weakness of muscles or groups of muscles due to compression of roots C-5, C-6, C-7, and C-8.

volvement of the eighth cervical root showed objective sensory changes and these were limited to the little and ring fingers. The digital pattern corresponded with that of subjective paresthesia for each root involved (figure 3); the area of objective change was frequently smaller than areas of paresthesia (figure 4).

INTERPRETATION AND COMMENT

General Data. Incidence. The incidence of involvement of the various cervical roots by a protruded disk in this series of cases, although admittedly a select group, agrees essentially with the findings presented by Spurling[1] for compressions of the fifth, sixth, and seventh cervical roots. Spurling found that in only 4 per cent of his cases did compression occur at the level of root C-8, compared to our finding of 10 per cent at this level, with a correspondingly lower incidence of involvement at the level of root C-6 (19 per cent) in our series.

Men are more apt to have a protruded cervical disk than women. All patients in Eaton's[2] and Michelsen and Mixter's[3] small series of surgically verified lateral protrusions were men. In Spurling's larger series 60 per cent were men and 40 per cent were women. Our series consists of 80 men and 20 women.

In our series the incidence of root compression on the left is 61 per cent and on the right 39 per cent. This dominance of left side over right side was seen in a number of other series,[3–6] but Spurling expressed the opinion that the incidence is almost equal for laterality.

In contrast to the confusion regarding diagnosis which existed prior to the report of Semmes and Murphey,[4] only one of our patients came to the clinic with a previously made diagnosis of coronary artery disease to explain the pain in his arm. This suggests that the point Semmes and Murphey made has been well accepted and the difference between pain in the arm due to protrusion of a cervical disk and that due to heart disease has been properly appreciated. However, in this series, one is impressed with the infrequency of pain in the anterior thoracic or pectoral region suggestive of an attack of coronary disease.

Increase in the total protein in the cerebrospinal fluid to more than 45 mg. per 100 cc. of fluid occurred in 40 per cent of our cases and there was no case of subarachnoid block. This incidence is similar to results reported by other investigators.[3,7,8]

TABLE 4

RELATION OF MUSCLE WEAKNESS TO COMPRESSION OF CERVICAL ROOT C-5, C-6, C-7, OR C-8

	Root compressed											
	C-5 (2 patients)			C-6 (19 patients)			C-7 (69 patients)			C-8 (10 patients)		
Muscle or group of muscles	*Number of patients*	*Degree of weakness, %*	*Percent of group*	*Number of patients*	*Degree of weakness, %*	*Percent of group*	*Number of patients*	*Degree of weakness, %*	*Percent of group*	*Number of patients*	*Degree of weakness, %*	*Percent of group*
Supraspinatus	2	60	100									
Infraspinatus	2	75	100									
Deltoid	2	75	100	3	30	16						
Brachioradialis	2	35	100	6	50	32						
Biceps	2	50	100	8	30	42	7	25	10			
Wrist extensors				7	30	37	13	25	19			
Triceps				5	25	26	45	50	65			
Finger flexors				4	25	21	8	40	12	5	40	50
Finger extensors							8	30	12	7	35	70
Interossei										7	35	70
Extensor pollicis longis										6	35	60
Hypothenar										5	35	50
Opponens pollicis										4	30	40

TABLE 5

PREDICTABILITY OF SIGNS AND SYMPTOMS REVIEWED IN A SERIES OF 100 PATIENTS

(Without Reference to Incidence)

	Signs and Symptoms													
	Pain in arm (when localized)		Pain in forearm (when localized)		Pain or paresthesia in hand		Subjective motor weakness		Objective motor weakness		Diminished reflexes		Objective sensory changes (hand)	
Localization of sign or symptom	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*	*No. of patients*	*Per cent*
Localized to one root	11	23	12	32	64	70	27	79	58	77	8	11	15	65
Localized to one of two roots	7	15	25	66	24	27	–	–	9	12	59	82	8	35
Conforms to different root pattern	3	6	1	3	3	3	7	21	5	7	2	3	0	–
Conforms to no pattern	26	55	0	–	0	–	0	–	3	4	3	4	0	–
Total patients	47		38		91		34		75		72		23	

Symptoms. Pain and Paresthesia. On the basis of our experience, the presence of pain in the neck, scapular and interscapular regions, or shoulder is of little value for localization of the level of compression of cervical roots. This symptom was present in cases in which roots C-5, C-6, C-7, and C-8 were compressed, except that scapular and interscapular pain was not present in the two cases with compression of root C-5. The incidence of pain in the neck is slightly higher when roots C-5 and C-6 are compressed than when roots C-7 and C-8 are involved. Interscapular and scapular pain is more frequent when roots C-7 and C-8 are compressed than when roots C-5 and C-6 are compressed. Pain in the shoulder is of slightly lower incidence when roots C-7 and C-8 are compressed. The presence or absence of pain in any of these regions is not of definite localizing value.[2,6]

In contrast to these findings, pain localized to the arm may be helpful in determining the level of the cervical root involved. If the pain is located posteriorly, it is most apt to be due to compression of root C-7; if it is medial, involvement of either root C-7 or C-8 is usually responsible. Pain in the lateral portion of the arm has been of little value by itself in determining the site of compression. From these observations one may conclude that pain in the arm localized to a specific region (47 per cent of our series) accurately indicated the site of compression to one root in 11 cases (23 per cent) and to one of two roots in seven cases (15 per cent); in 26 cases (55 per cent) it was of no localizing value. The location of pain in the arm did not conform to the expected pattern in three patients (6 per cent). Pain in the arm is, therefore, of minor importance in so far as accurate localization to one root is concerned. Authors previously have held the opinion that pain in the arm due to compression of root C-6 was located anterolaterally[3,6,7,9] and posterolaterally[10] and that such pain due to compression of root C-7 has been located posteriorly[10] and posterolaterally.[3,6,7,9] On the other hand, Davis, Odom, and Woodhall[8] stated that there was no characteristic localization of pain in the arm due to involvement of roots C-6 or C-7.

The location of pain and paresthesia in the forearm is of greater diagnostic significance in determining the root that is involved than is the fact that pain is present. However, as with pain in the arm, less than half of the patients (38 per cent) were able to localize their pain to a specific region of the forearm. Pain or paresthesia on the radial side of the forearm was found in instances of involvement of root C-6 or C-7 (seven with involvement of root C-6, nine of root C-7). Pain or paresthesia on the ulnar side of the forearm was present with lesions of root C-7 or C-8 (three of root C-7, six of root C-8). Pain located between the ulnar and radial aspects of the forearm (usually on the dorsum of the forearm) appeared to be caused by compression of root C-7. On the basis of these criteria, pain in the forearm or paresthesia when localized by the patient to a specific region in the forearm was correctly localized to one root in 12 cases (32 per cent) and to one of two roots in 25 cases (66 per cent). Only one patient showed involvement that did not conform to the expected pattern (3 per cent). Pain and paresthesia in the forearm, when present and localized by the patient, are primarily of value in determining the level of one of two roots being compressed and are rather reliable symptoms. Other authors have described pain or paresthesia in the forearm due to compression of root C-6 as located radially[3,5,6,10–12] or anteroradially.[9] Pain and paresthesia due to irritation of root C-7 have been described as located on the dorsum or extensor surface of the forearm.[3,5–7,9,10] Although the incidence of radial sensory symptoms is higher in compression of root C-6 (seven of 19 cases) than in compression of root C-7, radial sensory symptoms also occurred in our total group of patients having compression of root C-7 (nine of our 69 cases), making radial pain more characteristic of compression of root C-6 but only of localizing value for root C-6 or C-7.

The hand patterns of paresthesia (and, less often, pain) occur commonly; they are of great value in determining the specific root involved and occurred in all but nine patients in our series. Paresthesia limited to the thumb was always due to compression of root C-6. Involvement of the thumb and index finger, however, could not be used as evidence of involvement of root C-6 solely, because root C-7 also was involved in seven of the 18 patients having this digital pattern. Although this pattern (thumb and index finger) is most characteristic of involvement of root C-6 (11 of our 19 cases), yet, for purposes of localization to one root, involvement of root C-7 also must be considered. Paresthesia in the thumb, index and middle fingers, index alone, index and middle, middle and ring, or index, middle and ring fingers was present in 46 cases and in all but one it was due to compression of root C-7.

These symptoms, therefore, are very significant and of considerable localizing value. Paresthesia in the ulnar two or three digits was present in all ten cases owing to compression of root C-8, but the same sensory symptoms were present in three instances of compression of root C-7 and in one of root C-6. Paresthesia of the middle, ring, and fifth fingers must be considered a symptom suggesting involvement of root C-8, but the possibility that the symptom is due to irritation of root C-7 also should be entertained. Spasm of the scalenus anticus muscle may be responsible for this discrepancy in some instances, as suggested by Spurling[1] and others, and especially in our single instance in which compression of root C-6 caused this symptom. Paresthesia which was too poorly localized to be specifically designated or which spread to all digits was found in nine of 69 cases in which root C-7 was involved. Digital sensory symptoms were absent in nine instances, including both cases of compression of root C-5 and also cases in which lesions of roots C-6 and C-7 were found, so that the fact that digital symptoms are lacking is not in itself an indication of a lesion of root C-5.

On the basis of the afore-mentioned sensory symptoms, correct localization to a single nerve root can be made in 70 per cent of cases, and localization to one of two roots in 27 per cent; lack of conformity to the general pattern is noted in 3 per cent.

Some authors have described the sensory involvement of the thumb[10–12] due to a lesion of root C-6; others have described involvement of the thumb and index finger,[3,5] the thumb and often the thumb and index finger,[2,6,7] the thumb and index and middle fingers,[9] and predominantly the thumb and index finger but with other digits also involved.[8,13] The sensory pattern for compression of root C-7 has been described by Semmes and Murphey[4] and Elliott and Kremer[14] as affecting primarily the index finger. Other authors have stated that a lesion of root C-7 causes paresthesia in one or all of the three middle fingers,[5] in all of the finger tips,[6,7] in the index and middle fingers (also thumb and ring finger),[11] in index and middle fingers,[3,9,10,12] and in the index finger but also the thumb and middle finger.[2] Frykholm's[13] tables show that, when root C-7 is compressed, paresthesia most frequently involves the second and third digits, followed by the fourth and fifth digits; the table of Davis, Odom, and Woodhall[8] indicates paresthesia most commonly in the index finger, with the middle finger next most frequently involved. This variation, as found in our service, is reflected in figure 3.

Subjective Weakness. Subjective weakness in the involved upper extremity is present in about a third of cases (34 per cent) and the location of this subjective weakness is of some localizing value. In involvement of root C-5 the weakness is described in the shoulder; involvement of root C-6 resulted in weakness of the upper portion of the arm in five of the eight patients with subjective weakness. Diffuse or nonlocalized weakness in an upper extremity with involvement of nerve roots appears characteristic of compression of root C-7 (14 of 18 cases). In six of ten cases with compression of root C-8, subjective weakness was limited to muscles of the hand. On the basis that subjective weakness of the shoulder, upper part of the arm, diffuse upper extremity, and hand was an indication of compression of roots C-5, C-6, C-7, and C-8, respectively, correct localization of root compression can be made in 27 of 34 cases (79 per cent), with seven (21 per cent) not conforming to the pattern present in the majority.

Objective Findings. Reflexes. The information regarding muscle stretch reflexes is of considerable value in determining the site of cervical nerve-root compression. Seventy-two per cent of our series had reflex changes in the affected upper extremity. The most frequent finding was a diminution in the triceps reflex (51 cases, or 71 per cent of those with reflex changes). A diminished triceps reflex is not sufficient evidence to implicate the seventh root alone, since it was decreased in 65 per cent of the cases with involvement of root C-7 and in 60 per cent of those with lesions of root C-8. This finding in itself suggests involvement of either the seventh or eighth cervical root. Interestingly, although lesions of roots C-7 and C-8 cause a diminished triceps reflex, objective weakness of the triceps muscle is found much oftener when root C-7 is involved than when root C-8 is involved. This suggests that the efferent side of the reflex arc is primarily via root C-7 and the afferent side of the arc is via both roots C-7 and C-8.

Reduction of the triceps reflex in combination with a diminished brachioradialis reflex (four cases) or biceps (one case) was always due to involvement of root C-7 and is of value as a localizing sign for this root. A diminished biceps or brachioradialis reflex, alone or combined, was present in 13 instances, 11 of which were due to involvement of root C-6 (ten cases) or root C-5 (one case). A diminution

in the brachioradialis reflex alone appears to be significant in localizing involvement to root C-6. When all three reflexes are diminished in a specific patient, localization is not possible on this basis alone. Other investigators have suggested that a diminished triceps reflex indicates involvement of root C-7 and that a diminished biceps or brachioradialis reflex or both suggest a lesion of root C-6.[1,9,11,12] Davis, Odom, and Woodhall[8] found a high incidence of diminution of triceps reflex due to lesions of root C-7, but this finding also was present with lesions of root C-6 in their series. Frykholm[13] felt that changes in the triceps and biceps reflexes did not have any decisive value in establishing the level of a lesion. Michelsen and Mixter[3] stated that there were no significant differences in the diminution of biceps, triceps, or brachioradialis reflexes in different levels of cervical disk herniations.

On the basis of the foregoing criteria and when reflex changes were present, the lesions in 59 cases or 82 per cent could be correctly localized to one of two roots; in eight cases they could be correctly localized to one root (11 per cent), in three cases they could not be localized (4 per cent), and in two cases they did not conform to the majority pattern (3 per cent). Therefore, reflex changes are valuable for the localization of the cervical level for one of two roots. One might conclude that reflex changes alone are of relatively little value in localization to a single cervical root. Actually, inasmuch as compression of a seventh cervical root by a herniated disk is seven times as common as compression of root C-8, the finding of a diminished triceps reflex, especially in the presence of other evidence supporting a compression of root C-7, such as the finding of a weakened triceps muscle, strongly suggests a lesion of the seventh cervical root.

Objective Weakness. Weakness of single muscles or muscle groups is of great value in localization of a lesion to a single nerve root, in contrast to reflex changes which are mainly of value in localization of the lesion to one of two roots. Considerable difficulty arises, however, in the evaluation of weakness for localization, since in some instances there is objective weakness in several muscles or muscle groups. Our findings suggest that the weaker a muscle is the more significant it is for localization.

In both patients with involvement of root C-5 weakness was most striking in the deltoid, supraspinatus, and infraspinatus muscles. Involvement of the sixth cervical root frequently caused weakness most marked in the biceps, brachioradialis, and wrist extensor muscles. Weakness in the triceps muscle was most frequently noted when the condition was due to a lesion of root C-7. The intrinsic muscles of the hand (opponens pollicis, hypothenar, interossei), as well as the long flexor and extensor muscle groups of the fingers and thumb, were most frequently involved in lesions causing compression of root C-8.

Weakness of the deltoid with less severe weakness of the biceps muscle has been described in lesions of root C-5.[1,8] Other authors[1,11,12,14] have considered that weakness in the biceps, biceps and deltoid,[3,5,7] and biceps and triceps[8] was caused by lesions of root C-6. Lesions of root C-7 have resulted in weakness mainly in the triceps according to some authors,[1,5,11,12,14] but others[3,7,8] have included weakness in the biceps and deltoid also. Frykholm[13] stated that the finding of localized weakness is not of decisive value in establishing the segmental level of a radicular lesion. Most authors agree that lesions of C-8 cause most marked weakness in the intrinsic muscles of the hand.[1–3,7,14]

On the basis of our observations relative to muscle weakness the cause could be localized correctly to one root in 58 patients (77 per cent) and to one of two roots in nine patients (12 per cent); the root level could not be determined on the basis of objective weakness in three patients (4 per cent). Five patients (7 per cent) had weakness that did not conform to the pattern of the majority. In all cases in which root C-5 or C-8 was involved and in which objectives weakness was exhibited, the cause could be correctly localized.

Objective Sensory Changes. Objective sensory changes were not common but when present they were extremely valuable in localization. Only 23 patients had objective sensory changes in the hands, and the pattern corresponded with that described for subjective sensory complaints. In 23 patients having objective sensory changes in the hand, the cause could be localized to one of two roots in eight (35 per cent) and to a single root in 15 (65 per cent). Objective sensory changes were infrequent in our series in contrast to the findings of Keegan,[10] but when present they were extremely helpful for correct localization. It is interesting to note the close resemblance between the sensory findings in our series and those reported by Foerster,[15] who isolated single spinal roots and also noted the area of vasodilation following stimulations of individual dorsal roots.

GENERALIZATIONS AND CONCLUSIONS

Discrepancies from the usual clinical findings when a single cervical root is compressed, in addition to being caused by possible spasm of the anterior scalenus muscle or by coincidental disease of the peripheral nerves, might also be the result of variations in the roots taking part in the formation of the brachial plexus. In the authors' opinion, however, so-called prefixation and postfixation of the roots and plexuses relative to the vertebral column are of minor significance in accounting for clinical differences with respect to compression of a given cervical root. Many discrepancies would be eliminated if a more uniform precedure for obtaining the history were used and if the examination were carried out by persons cognizant of the symptoms and signs to be searched for; this is especially true as regards a precise history of the location of pain and paresthesia, as well as the results of that portion of the examination concerned with testing muscles.

Table 5 presents a summary of figures which demonstrate the predictability of various symptoms and signs in determining the level of cervical root involvement. The figures given represent, essentially, the number of cases in which each symptom and sign was exhibited and whether or not they conformed to a pattern which appeared to be characteristic for a specific root. Of necessity, certain criteria are made arbitrarily, but this table does show which symptoms and signs, alone and in combination, are most valuable in predicting the root involved in lesions of the fifth through the eighth cervical roots.

Table 5 shows that sensory symptoms and signs in the hand and motor changes in the entire upper extremity (subjective and objective) are highly significant in predicting the root involved, each category including more than 70 per cent of the cases.

As pointed out previously, although a diminution in a single reflex, for example the triceps, may not enable one to say whether root C-7 or C-8 is involved, this finding, when considered with other symptoms or signs, may be of great value in permitting specific localization to a single root. Of the various signs and symptoms, pain in the arm (as well as pain in the shoulders, scapular region, and neck) is of least value in localization.

Finally, in attempting to diagnose a specific root lesion, the experienced clinician will inevitably take into account the incidence of disk protrusion at the various levels. This factor, which is not given any consideration in table 5, must, consciously or otherwise, influence the final concept of the level of involvement.

A summary of the more salient and typical symptoms and signs for localization of compression of roots C-5 to C-8 is presented in table 6. The variations and exceptions to these findings, as discussed in this paper, are not reflected in this table. The clinician who attempts accurate localization of cervical root lesions on a clinical basis alone must be aware of the possible variations and frequent lack of positive findings in any given patient.

In retrospect and on the basis of the findings and interpretations discussed herein, cervical lesions could be localized correctly to a single nerve root in 87 of the 100 patients in this series and to one of two roots in ten of the patients; the signs and symptoms suggested a root other than the one actually involved in only three instances.

SURGICAL CONSIDERATIONS

The accurate and precise localization of surgical lesions of the nervous system is important. Because of the structures involved, it is especially important in the cervical region to limit the surgical exposure and operative procedures as nearly as possible to the presenting pathologic entity and the involved region. Sometimes diagnostic procedures present hazards which occasionally appear to be injurious. Thus, it was hoped that accurate clinical data could be accumulated which could be used to establish correctly the level of nerve-root compression so that surgery could be planned without such aids as myelography.

The identification of the single nerve root in-

TABLE 6

COMPRESSION OF CERVICAL ROOT: SUMMARY OF "TYPICAL" FINDINGS

Root	*Pain*	*Paresthesia in Digits*	*Muscle Weakness*	*Depression of Stretch Reflexes*
C-5	Not found distal to elbow	Absent	Shoulder	Biceps and brachioradialis
C-6	Radial aspect forearm	Thumb (and index finger)	Biceps, brachioradialis, and wrist extensors	Biceps and brachioradialis
C-7	Dorsal or volar surface forearm	Index and middle fingers	Triceps	Triceps
C-8	Ulnar aspect forearm	Little and ring fingers	Hand	Triceps

volved is desirable and seems to be reasonably expected as a result of our findings. However, the nature of the lesion may be obscure. Compression of a root might be due to protrusion of a disk, to arthritic ridging, or to a neoplasm. Clinical judgment of the history and results of examination usually are sufficient to determine the probability of occurrence of one of these entities. When surgical decompression seems indicated, however, it is important to decide whether surgical procedures should be limited to the extradural region or whether a more elaborate intradural exploration is to be anticipated. A spinal puncture of the lumbar subarachnoid space without introduction of Pantopaque or other contrast media seems desirable. If there is subarachnoid block as determined by manometric studies, or if the protein of the spinal fluid is markedly elevated, then one must anticipate more extensive investigation and possible intradural operation.

Thus, in the presence of a well-defined, isolated lesion of a cervical root, spinal puncture alone, without myelography, would appear to be a sufficiently accurate preoperative procedure. However, if clinical judgment and examination fail to disclose a lesion isolated to a single nerve root, or if the diagnosis cannot be accurately defined in this region by neurologic examination, myelography may be necessary. Occasionally one hesitates to explore even two cervical nerve roots to identify the site of the compression. Under these circumstances, the surgeon might wish to rely on myelography. However, it seems valid to us that, if the results of clinical examination suggest involvement of a single cervical root without involvement of the spinal cord and if examination of the spinal fluid suggests that there is not a tumor of the spinal cord, the surgeon can feel secure in planning the usual extradural procedure at the appropriate level.

SUMMARY

The symptoms and signs found in 100 patients with confirmed protrusions of single cervical disks treated and relieved by operation have been analyzed. In two cases root C-5 was involved, in 19 root C-6, in 69 root C-7, and in 10 root C-8.

Of all the findings reviewed, sensory symptoms or objective changes in the digits and localized muscle weakness were found to be the most reliable signs and symptoms for localization of the lesion to one root. Decreased activity in one or more of the major stretch reflexes of the upper extremity and localized pain in the forearm are highly significant in localizing the lesion to one of two roots.

Our study has revealed that an accurate history and reliable neurologic examination made it possible in 87 of 100 cases to predict correctly whether root C-5, C-6, C-7, or C-8 was compressed. If, in addition, lumbar puncture is carried out but does not show evidence of block or a markedly elevated value for total protein, it should be possible for the neurosurgeon to approach the compressed root directly and confidently without the aid of a preoperative myelogram, and, as a rule, to find that the cause of the root compression is a laterally protruded cervical disk.

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Direct Current Recordings of Eyeball Movements in Neurologic Practice

Robert Cohn, M.D.

WITH THE ADVENT of reasonably stable amplifiers capable of recording direct current potentials, it has become possible to obtain precise measurements of eyeball movements in clinical neurologic practice. Such precision recordings of eyeball movements are important adjuncts to the clinical neurologist, in that they allow detailed study of the physiology and pathophysiology of the eyeball movers. Moreover, recording facilitates the study of the degree and rate of recovery of eyeball movement following a disturbance of function. In clinical practice the rate, deviation, angle, and direction of gaze constitute important properties of eyeball movements. Consequently, when the rate of eyeball movement is slow or when the maintenance of a given deviation of the eyeballs is an important aspect of the study or when the absolute directions of the eyeball deviation are necessary data, it is imperative to utilize amplifiers capable of recording slow variational, or steady, potentials with fidelity.

METHOD

The Offner type 142-DC amplifier and dynograph system was used to obtain all the material of this presentation. A large number of the pen recordings were controlled by cathode ray oscillograph tracings. The 142-DC amplifiers have been in operation in this facility for over six years. With proper voltage regulation and well balanced tubes, the DC drift in this recording system was negligible, as observed in the chart calibrations, for the sensitivity and time durations utilized.

Electrodes consisted of two types, calomel half-cells and solder pellet-electrode paste combinations. The calomel electrodes were two half-cells (Pt-Hg- (Hg-Hg_2Cl_2)-KCl) enclosed in a short length of polyethylene tubing. This electrode assembly was applied to the periorbital regions by individual adjustment from a specially constructed carrier. A much simpler electrode in application and construction was the solder pellet-NaCl-electrode jelly-bentonite combination. Small bits of the electrode paste mixture were applied to the external and internal canthus of each eye; the 4 mm. diameter solder pellet was then placed over the paste and fixed into position with collodion. This simple derivation system proved eminently satisfactory in all ways. At the start of each recording baseline drift and other instabilities (sweat activities) were manifest, but these drifts disappeared usually within ten minutes and very proper tracings were obtained. The pick-up was fed into the amplifiers in a tandem array so that the positively charged cornea moved toward grid I of each amplifier with conjugate eyeball deviation; by this arrangement, the recordings appeared in the same direction as the eyeball movements. Deviation angles of eyeball movements were estimated with a portable perimeter.

RESULTS

Normal eyeball movements of approximately 50 degrees maximum lateral deviation from forward gaze, as recorded with direct current amplifiers, are depicted in figure 1. With conjugate eyeball movements in either lateral gaze, an approximate square wave of potential was recorded. It was interesting that unequal potential differences were recorded in either lateral gaze, despite essentially equal angles of conjugate eyeball movement. Ordinarily the right eye in right lateral gaze and the left eye in left lateral gaze showed a 10 to 15 per cent increase in amplitude, as compared with the right eye in left gaze and the left eye in right gaze. That is, each eye in temporal gaze generated greater potentials than in nasal gaze. These amplitude differences were believed due to the necessary asymmetry of electrode placements. It is obvious, of course, that the right-left differences might have resulted from unequal excursions of the eyeballs that could not be determined by hand perimeter angle measurements.

As indicated in figure 1, convergence was manifest by relatively slowly converging potentials. The amplitude differences in the convergence action were quite common. The superimposed pips in the basic deflections were due to eyelid blinking movements.

The critical importance of symmetry and the distance from the eyeball of the electrodes was shown by experiments exemplified in figure 2. Here electrodes were separately arrayed one-half inch between centers, beginning at the

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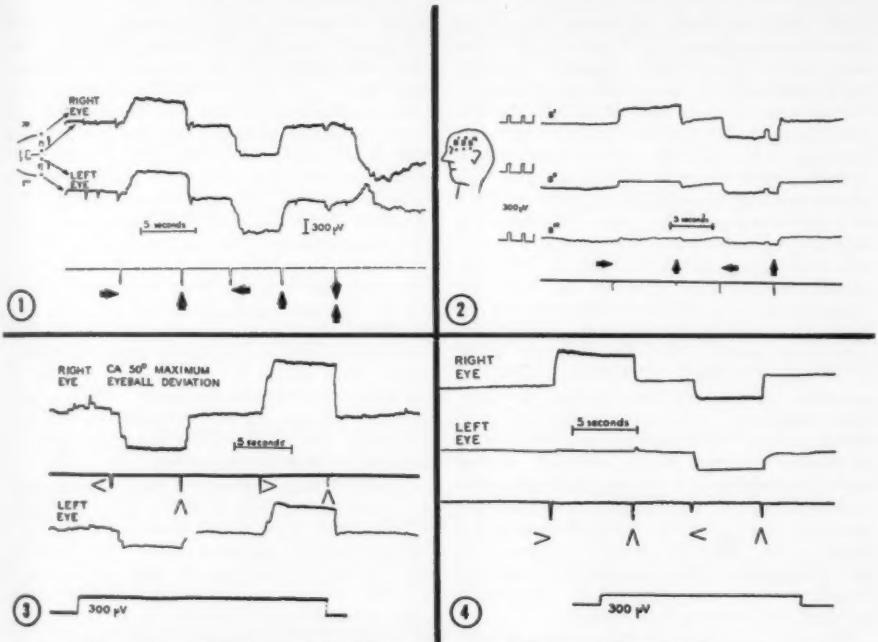

FIG. 1. Normal eyeball movements. Note the greater amplitudes in each temporal gaze.
FIG. 2. Effect of electrode position on potential output
FIG. 3. Injured left eye. Decreased electric output as a result of damaged neural network.
FIG. 4. Left internal rectus paralysis.

outer canthus. An over two-fold decrease in voltage was obtained with each half inch increment from the canthus reference point. From these data it is apparent that valid serial studies must assiduously maintain identical pick-up areas, particularly if the absolute amplitude property is important.

Although in a given set of measurements the amplitude of potential was primarily dependent on the angle of eyeball deviation from forward gaze, the functional integrity of the eye was also an important factor. This is shown in figure 3 where the conjugate deviation angles, although essentially equal, generated an approximately two-fold increase of recorded potential in the normal right eye as compared with the output of the amaurotic left eye. This latter bulb was rendered non-functional by absolute corneal and lenticular opacities resulting from trauma approximately ten years prior to this examination. That primary or secondary damage to the potential generating system was sustained was evident from the fact that, if only the refractive structures were involved, an effect similar to that obtained when an eyelid is closed would have been observed. Ordinarily, when the normal eye is closed, for a given angle of eyeball deviation, there is at least a 5 to 15 per cent increase in the amplitude of the generated potential.

Figure 4 represents the zero electrical output obtained with complete paralysis of the left eye in right gaze. Each eye was equally effective for left gaze, but the left eye in temporal gaze did not show the usual increased amplitude. This type of finding was not general, but was sufficiently frequent to invite the idea that the total output potential of certain eyes was partially dependent on the integrity of all eyeball movers.

A paretic eyeball mover was, or course, manifested by decreased recordable potential. This is shown in figure 5. Due to the decreased angle of deviation of the right eyeball as the result of an abducens nerve lesion, a decreased amplitude of potential was recorded during the attempt to perform a right lateral conjugate movement. It should be observed that the potential of the right eye in left gaze was of lower amplitude than that of the left eye in right

gaze. This amplitude difference was of the same order as observed in figure 4. The upper two lines of figure 5 were obtained with fairly rapid positioning of the eyeballs in lateral gaze. The next pair of lines were obtained with slow positioning of the eyeballs. In these latter recordings, although the eyeball movements seemed almost smoothly continuous, the electrical recordings showed the movements to be of a discontinuous, jerky type. This same patient showed almost complete recovery of eyeball movement function in figure 6. The amplitude asymmetries were of the type described earlier. It should be observed that the right eye in left gaze generated a higher amplitude of potential than for the same angle of movement in figure 5. Again, the jerky, or saccadic, action with slow eyeball deviation was recognized. This was particularly well shown in the second pair of lines with only a 45 degree deflection of the eyeballs. In this pair of recordings the saccades indicate a resolution ability of the amplifier and recording system at the sensitivity used of around 2.5 degrees. The saccadic eyeball movement in slow positioning of the eyeballs was a general phenomenon; it was observed in all patients in which such testing was studied.

Figure 7 was obtained from a patient with an incomplete medial logitudinal fasciculus syndrome. He was unable to deviate the right eye to the left and only partially able to deviate the left eye to the right, but he was able to converge the eyes. Part A of the figure shows the electrical concomitants of this clinical phenomenon. The amplitude of output of the left eye was diminished in right gaze; in left gaze the right eyeball showed no potential variation (because of the eyeball fixation); in convergence a converging potential difference was observed. The right eye in right gaze showed a slow nystagmoid activity in maximal eyeball deviation that was not clinically discernible. In B of the same figure partial recovery was achieved. The maximum amplitudes of the right eye movement to the right and the left eye to the left persisted, as did the diminished left eye output in right gaze, but a definite potential was recorded from the right eye in left gaze. The convergence response was slow and not well defined during this recovery phase.

Figure 7B also shows the inadequacy of recording eyeball movements with amplifiers capable of recording only relatively rapid variations in potentials (even with one second time constants). It is observed that the amplitudes of movements are approximately equal in the AC and DC recordings. However, the first deflection in the AC recording (third line) was lower in amplitude than the corresponding DC amplitude in the first line, because the rise time of the eyeball movement was too slow for the AC amplifier to record with fidelity. Although under ideal conditions the amplitudes may be equal in AC and DC recordings, the *absolute* directions of eyeball movement cannot be determined from AC recordings. Thus, in the third line (AC recording), the first negative deflection resulted from the simple return of the deviated eyeballs to the forward rest position. Moving the same eyeball to the left resulted in another negatively recorded deflection. With return to the neutral position a positive potential was produced. As a consequence, the sign of the potential in the AC recording cannot determine the gaze position attained by eyeball movement.

Vertical plane movements may be measured by placing electrodes in that plane. In figure 8, electrodes were placed in both the horizontal and vertical planes to study the possible interaction, or coaction, of these movements. Eyeball movements in upward and downward gaze evoked approximately equal amplitudes of potential. This symmetry again appeared to be a function of electrode placement. It was observed that with upward movement a very minimal lateral movement to the right occurred simultaneously; with downward gaze there was a considerable deviation of the eyeball to the left. These deviations appeared to be related to the coaction of the oblique muscles in maximum eyeball movements in the vertical plane. In eyeball movements to lateral gaze, the simultaneous vertical plane recordings showed less interaction than observed in figure 8, but definite interaction did occur.

Nystagmus, because of its relatively rapid variational character, can be measured easily with AC amplifiers. Instruments capable of recording DC variations, however, show in a much more effective way the angle of lateral gaze (or vertical) deviational gaze necessary to attain before nystagmus becomes manifest. Such a record is shown in figure 9. The nystagmus is shown to occur at approximately a 30 degree deviation in this patient who had a cerebellar disorder. In this individual it was also observed that convergence resulted in slow repetitive actions.

DISCUSSION

The recording of eyeball movements with direct current amplifiers has proved feasible

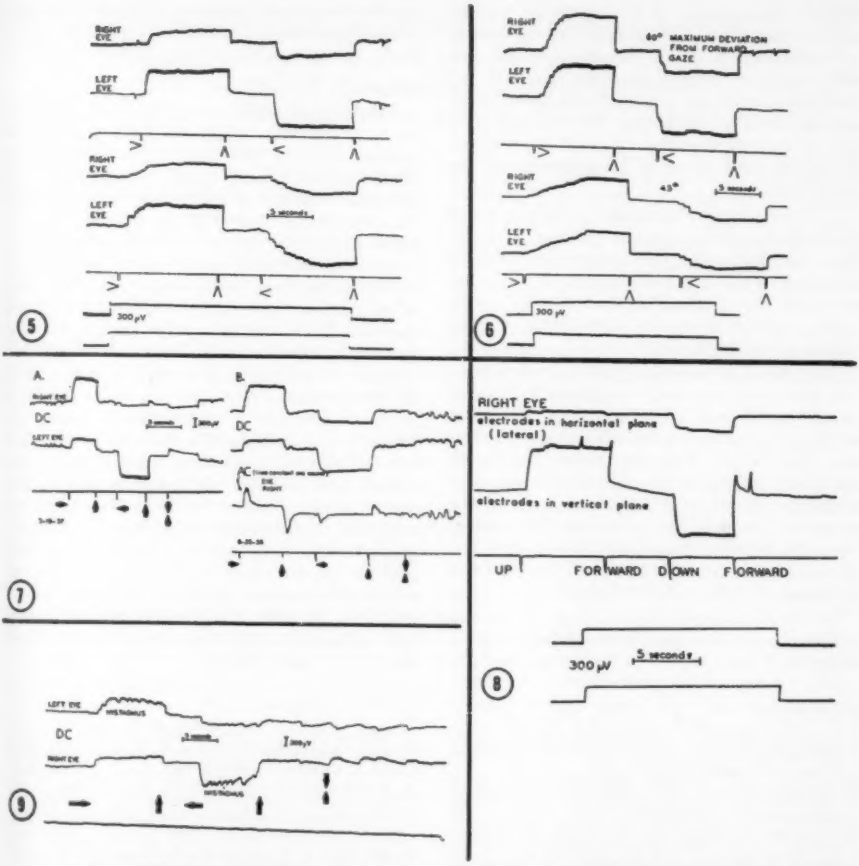

FIG. 5. Right abducens paresis. Lower pair of tracings show saccadic action with slow positioning of eyeballs in maximum lateral gaze.
FIG. 6. Recovery from right abducens paresis.
FIG. 7. *A.* Medial longitudinal fasciculus syndrome. *B.* Partial recovery *AC* recording of right eyeball movement.
FIG. 8. Simultaneous horizontal and vertical plane measurements of right eye, normal.
FIG. 9. Nystagmus measurements with DC amplifiers.

and practical for use in clinical neurology. Several authors[1–3] have earlier indicated the possibility of using DC recordings of the eyeball for such purposes; however, their published works pertain primarily to recordings under experimental conditions. Most of the work pertaining to clinical material has treated of spontaneous and opticokinetic nystagmus.[2,4,5]

Mowrer, Ruch, and Miller[6] first clearly showed that the "standing" potentials recorded from the eyeball were intrinsic to the nervous network of the eyeball and not a phenomenon of muscle action potentials. In man and other warm-blooded animals the cornea is positive with respect to the retina. Thus the eyeball may be represented as a sphere with a positive and negative pole. The movement of this polarized sphere with respect to a fixed reference (electrodes) is responsible for the observed potential changes.

It has been shown that the steady potentials recorded from a fixed reference were proportioned to the angle of deviation of the eye-

ball.[7,8] Consquently, if in any given individual the magnitude and polarity of the potential difference in lateral deviation of the eyeball is plotted against the simultaneously recorded potential difference derived from supra- and infraorbital electrodes, the eyeball position in two dimensional space is determined. This holds most precisely for submaximal eyeball deviations.

In direct current recordings the *rate* at which the eyeball attains a given position in space does not determine the amplitude potential difference. The sole determinant of the magnitude of potential, under fixed normal conditions, is the angular deviation of the eyeball from a given reference.

The failure of very nearly equal angle right and left lateral eyeball deviation to develop almost equal potential differences has been ascribed to the necessary asymmetry of electrode placement. This was arrived at as the result of studies showing the critical nature of electrode placement on the amplitude of the recorded potentials. It is possible that another factor for the amplitude asymmetries might be the noncongruent orientations of the electrical and binocular forward gaze axes.

The measurement of gaze angle by means of a hand perimeter gave a precision of hardly better than 5 degrees. To make more precise measurements of angle of eyeball deviations would have taken the method out of the reach of routine practice.

SUMMARY

The eyeball, which is a spherically polarized body, maintains a relatively fixed potential of around 500 to 800 microvolts between the retina (positive) and cornea (negative). This potential difference which is conducted through the periorbital tissues is recordable between fixed electrodes. With eyeball movement a variational potential is recorded with respect to the periorbital fixed electrodes. The rate of recordable potential variation is a direct function of the rate of eyeball movement, but the amplitude of recorded potential is a direct function of the angle of eyeball deviation from its rest position. When the eyeball moves and remains in its new fixed position, a steady potential is recorded for the duration of the fixation. If the eye movement mechanism is disturbed from any cause and the deviations in a plane parallel to the electrode placement are restricted, the potential difference recorded is proportional to the angle of deviation accomplished. In the absence of movement no potential difference is recorded. With the use of amplifiers capable of recording steady potentials, clinically important details of eyeball movement were studied.

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Hypothalamic Seizures From Stimulation of Rhinencephalon and Isocortex in Cat

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THERE HAS BEEN very little work done on hypothalamic seizure activity following stimulation of subcortical and cortical epileptogenic foci. Consequently, the origin of hypothalamic epileptoid activity is still obscure. If one assumes that the hypothalamus is the principal center for cerebral outflow to lower autonomic neurons, it becomes important to know how the hypothalamus itself may be influenced by higher level autonomic structures.

The present paper is not concerned with the complete distribution of epileptogenic foci throughout the subcortex and cortex, but primarily with the possibility of producing epileptoid activity in the hypothalamus experimentally. From Gloor's work[1] it is evident that single shock stimulation of the amygdala produces responses in the hypothalamus. From previous work done in our laboratory,[2] stimulation of the amygdaloid nucleus, hippocampus, and pyriform cortex produces responses in the hypothalamus. Other unpublished data on single shock stimulation indicate that the hippocampal gyrus, septum, dorsal hippocampus, and anterior olfactory areas project directly or indirectly to the hypothalamus. Accordingly, certain sites were selected for stimulation on the basis of their known hypothalamic connections, on the theory that structures which in some way affect the hypothalamus from single shock stimulation would most likely produce epileptoid activity in the hypothalamus.

In this survey the lateral and posterior extensions of the lateral amygdaloid nucleus, hippocampus, hippocampal gyrus, septum, and anterior olfactory areas were stimulated. Cortical areas of the dorsolateral surface were also stimulated, since the role of the cortex in the production of hypothalamic activity has been studied only incidentally by other authors.

METHOD

Young adult male cats were used for the experiments. The experiments were performed on animals anesthetized with Nembutal (1 cc. of 3.5 per cent solution per kg.) and on animals anesthetized locally with procaine (2 per cent), followed by D-tubocurarine chloride (3 mg. per cc. intravenously) until respiration ceased, and then maintained by artificial respiration plus oxygen flowing at the rate of three liters per minute. Concentric bipolar stimulating and recording electrodes were used, except for the cerebral cortex in which bipolar silver wire electrodes were employed. A 3C Grass square-wave stimulator was used to deliver stimuli each having a pulse duration of one millisecond. Hypothalamic and other potentials were recorded by a 3D Grass electroencephalograph.

The routine location of three hypothalamic pickup leads is shown in figure 1A, B, and C. The electrodes were three millimeters apart and were located in the medial preoptic area (figure 1A), in the ventromedial hypothalamic nucleus (figure 1B), and in the mammillary body (figure 1C). Placement of electrodes in the brain was verified in frozen serial sections stained by Windle's[3] buffered thionin method.

RESULTS

A normal hypothalamic record is characterized by asynchronous waves of low voltage (20 to 60 microvolts), as compared with a normal record taken from the motor cortex (100 to 250 microvolts) (figure 2A).

Stimulation of lateral amygdaloid nucleus. The location of the stimulating electrode in the lateral amygdaloid nucleus is indicated by the solid circle in figure 1D. A record taken from the hypothalamus following stimulation of the lateral amygdaloid nucleus is shown in figure 2B. Following stimulation, a hypothalamic discharge lasting for 17 seconds occurred. It consisted of high and medium spike potentials. The highest potentials (200 microvolts) were recorded from the ventromedial hypothalamic nucleus. Lower potentials were recorded from the preoptic and mammillary body, both of which seem to reflect the activity of the ventromedial nucleus.

Stimulation of the posterolateral amygdaloid nucleus. The location of the stimulating electrode in the posterior extension of the lateral amygdaloid nucleus, together with an adjacent monitoring pickup lead in the anterior pole of

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This work has been supported by grant B-1046 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health.

the hippocampus, is shown in figure 1E. Repeated seizure records obtained from the hypothalamus after stimulation of the posterolateral amygdala are represented by records shown in figure 2C and D. In the second channel of record C there is an initial spike response from the ventromedial hypothalamic nucleus. In the third channel a gradually increasing response from the mammillary body can be correlated with the very high and sustained response from the hippocampus recorded in the fourth channel. In record C-1 the mammillary body is not in harmony with the high voltage activity of the ventromedial nucleus, nor is it in harmony in record C-3 in which the ventromedial nucleus is low, while the mammillary lead is higher and in close harmony with the fast spike potentials of the hippocampus. This suggests a direct amygdalo-hypothalamic relationship and an indirect response of the mammillary body by way of the ictal activity of the hippocampus, rather than an intrahypothalamic mechanism.

In our experience, we have noted a considerable degree of variability in phase, amplitude, frequency, wave-form, and duration of seizure activity recorded from the hypothalamus, so that any single record should not be considered as a stereotype. For example, in figure 2 record C-1, which follows stimulation of the posterolateral amygdaloid nucleus, the ventromedial nucleus exhibits spike potentials. In record D-1 repetition of the stimulation at the same parameter resulted in a 38-second run of spike-wave potentials. Some seizures may exhibit consecutive prodromal, tonic, and clonic phases with an abrupt termination; others, such as some of those illustrated in figure 2, may be lacking in one or the other of these phases. To what factors this variability can be attributed we are not now able to say.

As can be noted from numbers 182 and 116 at the end of records C and D, the duration of the seizure activity was much longer in seizures originating from the posterior portion of the lateral amgdaloid nucleus, than in those originating from stimulation of the more anterior portion of the lateral amygdaloid nucleus (figure 2B).

Stimulation of hippocampus. In the cat the hippocampus has a twofold location. One portion is located ventrally in the temporal lobe (figure 1F); the other is the continuation of the ventral part posteriorly, dorsally, and forward to its location next to the midline and above the anterior midbrain region (figure 1G).

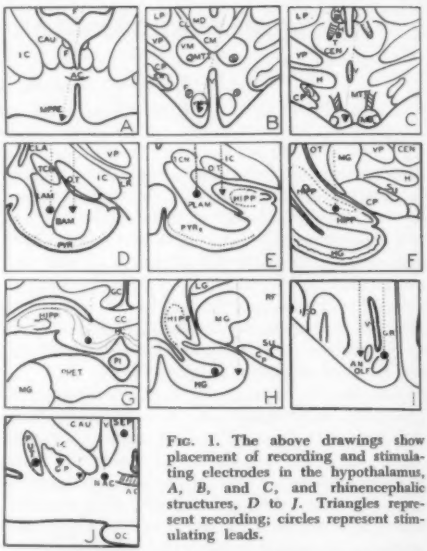


FIG. 1. The above drawings show placement of recording and stimulating electrodes in the hypothalamus, *A*, *B*, and *C*, and rhinencephalic structures, *D* to *J*. Triangles represent recording; circles represent stimulating leads.

Abbreviations: AC-anterior commissure; ANOLF-anterior olfactory nucleus; BAM-basal nucleus of amygdala; CAU-caudate nucleus; CC-corpus callosum; CEN-centre-median nucleus; CL-central lateral nucleus of thalamus; CLA-claustrum; CM-central median nucleus of thalamus; CP-cerebral peduncle; EN-entopeduncular nucleus; F-fornix; GC-gyrus cinguli; GP-globus pallidus; GR-gyrus rectus; H-fields of Forel; HB-habenular nucleus; HBT-habenulopeduncular tract; HC-hippocampal commissure; HG-hippocampal gyrus; HIPP-hippocampus; IC-internal capsule; ISO-isocortex; LAM-lateral nucleus of amygdala; LG-lateral geniculate body; LP-posterior lateral nucleus of thalamus; LR-lateral reticular nucleus of thalamus; MB-mammillary body; MD-dorsomedial nucleus of thalamus; MG-medial geniculate body; MPRE-medial preoptic nucleus; MTT-mammillothalamic tract; NAC-nucleus of anterior commissure; OC-optic chiasma; OT-optic tract; PLAM-posterior part of lateral amygdaloid nucleus; PI-pineal body; PRET-pretectum; PUT-putamen; PYR-pyriform cortex; SEP-septum pellicidum; SU-subthalamic nucleus; TCN-tail of caudate nucleus; V-ventricle; VM-ventromedial nucleus of thalamus; VMH-ventromedial nucleus of hypothalamus; VP-ventral posterior nucleus of thalamus.

Stimulation of the ventral and dorsal portions of the hippocampus produces different ictal effects in the hypothalamus. Stimulation of the ventral hippocampus produced marked high potentials in the ventromedial hypothalamus and lower but prominent potentials in the mammillary body (figure 2E). Stimulation of the dorsal hippocampus produced its principal ictal activity in the mammillary body, and the overall amplitude was less than that following stimulation of the ventral hippocampus. The preoptic and ventromedial hypothalamic regions exhibited only very low and belated ictal effects (figure 2F). The termination of hypo-

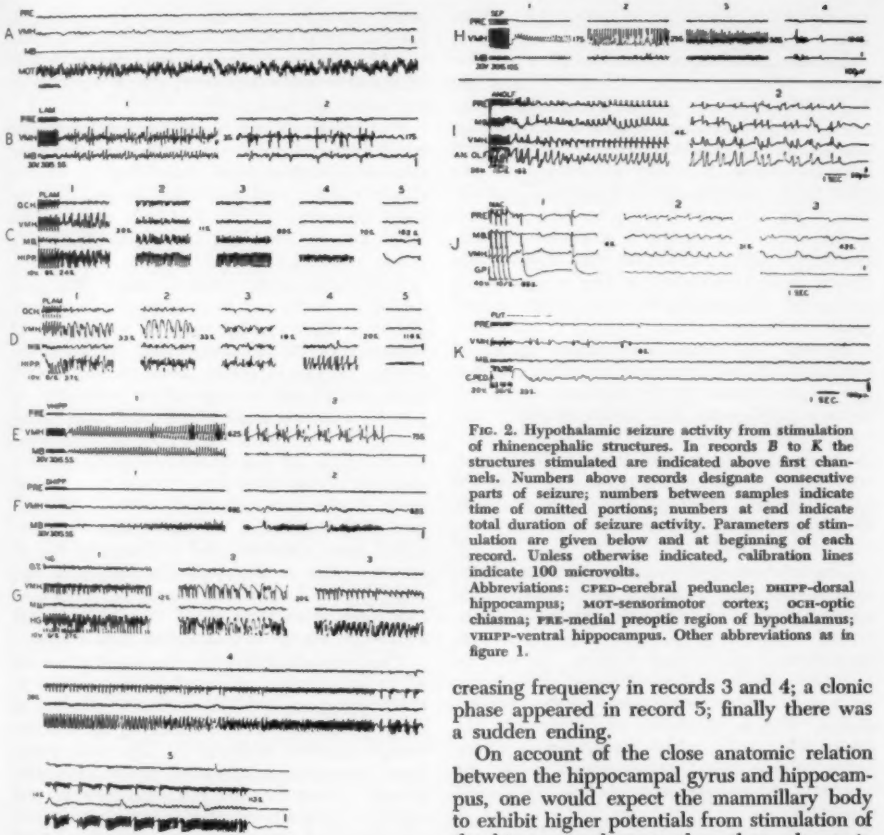


FIG. 2. Hypothalamic seizure activity from stimulation of rhinencephalic structures. In records *B* to *K* the structures stimulated are indicated above first channels. Numbers above records designate consecutive parts of seizure; numbers between samples indicate time of omitted portions; numbers at end indicate total duration of seizure activity. Parameters of stimulation are given below and at beginning of each record. Unless otherwise indicated, calibration lines indicate 100 microvolts.
Abbreviations: CPED-cerebral peduncle; DHIPP-dorsal hippocampus; MOT-sensorimotor cortex; OCH-optic chiasma; PRE-medial preoptic region of hypothalamus; VHIPP-ventral hippocampus. Other abbreviations as in figure 1.

thalamic seizures, following stimulation of the dorsal and ventral portions of the hippocampus, was usually preceded by a clonic phase (figure 2E and F).

Stimulation of hippocampal gyrus. The hippocampal gyrus (figure 1H) was found to be productive of hypothalamic seizure activity. The record of a single hypothalamic seizure (figure 2G, records 1 to 5) was obtained from stimulation of the hippocampal gyrus at the same parameter used for stimulating the posterolateral amygdala (figure 2C and D). Following stimulation of the hippocampal gyrus, the ventromedial hypothalamic nucleus exhibited the highest potentials of the hypothalamic leads. The character of the record changed as the activity progressed. Monophasic spikes in record G1 (VMH) became spike-wave in record 2; then followed a spiking period of increasing frequency in records 3 and 4; a clonic phase appeared in record 5; finally there was a sudden ending.

On account of the close anatomic relation between the hippocampal gyrus and hippocampus, one would expect the mammillary body to exhibit higher potentials from stimulation of the hippocampal gyrus than those shown in record G. The record suggests that impulses from the hippocampal gyrus may bypass the hippocampus and project directly or indirectly to the hypothalamus. The electroencephalogram indicates this, since ictal activity of the ventromedial nucleus of the hypothalamus promptly changed whenever a change occurred in the hippocampal gyrus.

Stimulation of the septum. Records of seizure activity of the hypothalamus could be obtained readily from stimulation of the septum. Location of the stimulating electrode is shown in figure 1J. A hypothalamic record following stimulation of the septum is shown in figure 2H. As can be noted, very high potentials of some 250 microvolts appear in the ventromedial nuclear lead. The preoptic and mammillary leads have very low potentials and possess no distinctive indication that they

are doing any more than mirroring the activity of the ventromedial lead.

Stimulation of basal frontal structures. The anterior olfactory nucleus (figure 1I) and the bed nucleus of the anterior commissure (figure 1J) did not produce seizure activity as vigorously in the hypothalamus as did temporal lobe structures. A record of seizure activity from the hypothalamus obtained from stimulation of the anterior olfactory nucleus is shown in figure 2I. The activity is of slower frequency and of shorter duration than activity obtained from stimulation of the posterolateral amygdala, hippocampus, and hippocampal gyrus.

Record J of figure 2 illustrates epileptoid discharge obtained from the hypothalamus following stimulation of the nucleus of the anterior commissure. Only slight and poorly sustained discharge was produced in the hypothalamus, despite the fact that good responses were obtained during stimulation. Stimulation of the putamen produced only a few relatively low voltage spike potentials in the hypothalamus (figure 2K).

The ventromedial nucleus. In most of the experiments the ventromedial hypothalamic nucleus responded most prominently to stimulation of the amygdala, ventral hippocampus, hippocampal gyrus, and septum. As will be presently shown, it also responded prominently to stimulation of certain areas of the cerebral cortex. Figure 2F shows one exception, the mammillary body, which responded to stimulation of the dorsal hippocampus, while the ventromedial nucleus and preoptic leads were negative.

According to Ingram,[4] who reported on Wheatley's work,[5] removal of the ventromedial nucleus produces rage and its integrity is considered necessary for the inhibition of rage. Stimulation of this nucleus results in complex sympathetic discharge.[6] Anatomic evidence shows[7] that it receives fibers from the amygdala and tip of the temporal lobe. In keeping with its varied afferents it has a multiple cytologic character. Brockhaus[8] has described magnocellular, mediocellular, and parvocellular components in the human ventromedial hypothalamic nucleus.

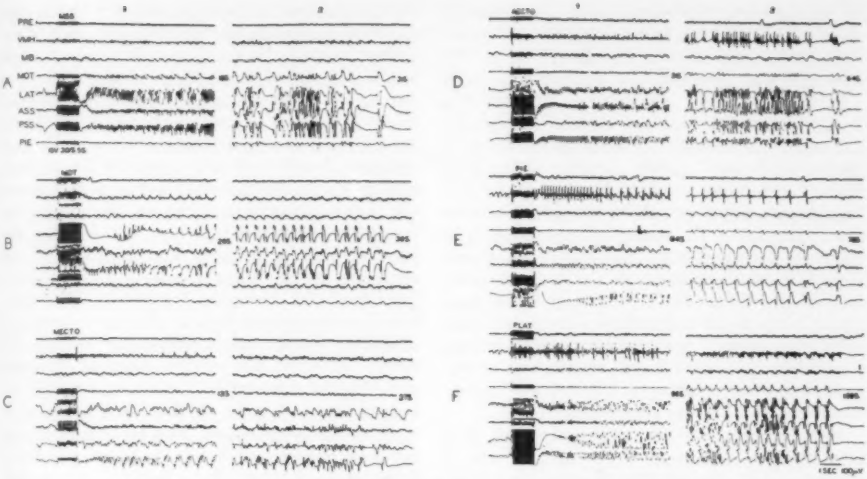
In view of the ease with which ictal activity can be recorded from the ventromedial hypothalamic nucleus from stimulation of such a variety of structures (see above), it is likely that these higher level structures may differentially affect the function of the ventromedial nucleus to produce degrees of anger or to suppress its actvity. The latter seems to be the case since bilateral removal of basal temporal structures,[9] including the amygdaloid nuclei, results in placidity and compulsive, gregarious mating tendencies in the animal.

Our results do not provide specific evidence for differential physiologic effects on the ventromedial nucleus from stimulation of various rhinencephalic and isocortical areas. The results, however, confirm that it is a prominent focal area for the reception of autonomic impulses from high level structures.

Stimulation of the cerebral cortex. The present study is limited to epileptoid effects produced in the hypothalamus by stimulation of cortical areas on the dorsolateral surface of the brain. All the principal areas of this surface were stimulated in each of six cats, two of which were unanesthetized and four anesthetized. A constant parameter of stimulation of 15 volts, 30 per second frequency, for a duration of five seconds was used to stimulate areas in the unanesthetized animal. Stimulation of the cortex in unanesthetized cats provided more clear-cut and prolonged ictal responses. Use of this particular parameter and none higher limited the factor of spread, so that some areas were found to have a greater ictal effect on the hypothalamus than others.

The general distribution of cortical sites from which stimulation produced positive effects in the hypothalamus is shown in the drawing of the cerebral cortex accompanying the electroencephalograms in figure 3. The most prominent responses, as indicated by the large solid triangles, were obtained from the posterior and anterior ectosylvian, posterior suprasylvian, and posterior and inferior portions of the lateral gyri. Remaining areas on the dorsolateral surface were either negative or much less active than those listed above, as indicated by the small solid triangles in the drawing.

Figure 3A to F shows records of the hypothalamus and cerebral cortex following stimulation of the dorsolateral cortical surface in the unanesthetized cat. Records A, B, and C show the negative or very poor ictal effects in the hypothalamus from stimulation of the middle suprasylvian (A), sensorimotor (B), and middle ectosylvian (C) gyri. Stimulation of the middle suprasylvian gyrus produced negative results, except that the over-all amplitude was slightly increased when compared with the prestimulatory record of the hypothalamus. Stimulation of the sensorimotor and middle ectosylvian gyri produced a few, unsustained spikes of medium amplitude in the ventromedial hy-



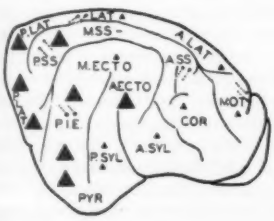


FIG. 3. Effects of stimulation of nontemporal, *A*, *B*, and *C*, and temporo-occipital cortex, *D*, *E*, and *F*, on the hypothalamus. In drawing below electroencephalograms, small triangles indicate cortical areas least effective in producing hypothalamic seizure activity (records *A*, *B*, and *C*). Large triangles indicate cortical areas most effective in producing hypothalamic ictal effects (records *D*, *E*, and *F*). Area stimulated, parameter, and duration of seizures are indicated as in preceding figures. The location of the bipolar cortical pick-up leads as listed in record *A* are indicated in the accompanying brain diagram by the oblique paired dotted lines.

Abbreviations: AECTO-anterior ectosylvian gyrus; ASS-anterior suprasylvian gyrus; LAT-lateral gyrus; MECTO-middle ectosylvian gyrus; MSS-middle suprasylvian gyrus; PIE-posterior inferior ectosylvian gyrus; PLAT-posterior lateral gyrus; PSS-posterior suprasylvian gyrus. Other abbreviations as in preceding figures.

pothalamus, even though cortical seizure activity was of high amplitude.

Records D, E, and F of figure 3 show prominent seizure discharge in the ventromedial hypothalamic lead following stimulation of the anterior ectosylvian gyrus (D), the middle and inferior portions of the posterior ectosylvian gyrus (E), and the posterior portion of the lateral gyrus (F). The seizure activity resulting from stimulation of the above temporal areas and adjacent posterior portions of the lateral and suprasylvian gyri was of longer duration than that elicited from other areas previously described, as indicated by numbers at the end of the records. The hypothalamic seizure activity was characterized by sharp spike discharges of high amplitude and was sustained to the cessation of the cortical ictal activity.

When a low parameter of short duration was used in the unanesthetized cat, areas other than the more active temporal and occipital regions produced very weak potentials in the hypothalamus and there was no evidence of spread from these areas of the cortex to the more active ones. When higher parameters were used, the "weaker" areas produced low rolling waves in the hypothalamus. In these cases, if the stimulated cortex continued firing, spread to other areas occurred. Only when the spread of cortical activity implicated the temporal region did the character of the hypothalamic activity promptly change from a low rolling type to high, fast, spike activity.

Stimulation of the dorsolateral cortical surface was also carried out on animals anesthetized with Nembutal (0.75 to 1 cc./kg.; 3.5 per cent). A stimulating parameter of 40 volts, 30 per second, for durations varying from 5 to 30 seconds was needed to produce even slight effects in the hypothalamus. However, even though cortical stimulation in the anesthetized cat produced ictal activity of less intensity than in the unanesthetized cat, the same pattern of results was obtained.

The anatomic gyri whose stimulation evoked seizure activity in the hypothalamus can be

correlated with Brodman's areas. The inferior portion of the posterior ectosylvian gyrus (P.I.E.) corresponds to Brodman's areas 20 and 22; the posterolateral (P.LAT.) to area 17; the posterior suprasylvian (P.S.S.) to areas 18 and 19; and the middle ectosylvian (M.ECTO.) to area 41, as outlined by Krieg.[10] Stoll and his associates[11] considered the posterior ectosylvian gyrus of the cat to be the homologue of the tip of the temporal lobe in the primates. In their electrophysiologic studies of this region, two-way connections were found to exist between the posterior ectosylvian gyrus and the septum and basal ganglia. Corticofugal connections only were made with the medial and lateral hypothalamus. From this, it is possible that stimulation of the posterior ectosylvian gyrus produces direct ictal effects in the hypothalamus.

In the drawing accompanying figure 3, it is interesting to note that stimulation of visual (P.LAT) and visiopsychic (P.S.S.) areas produced vigorous seizure activity in the hypothalamus. The question is thereby raised whether photic stimulation, used experimentally and clinically to precipitate seizures, has autonomic effects.

The prominent and sustained hypothalamic seizure activity produced by stimulation of temporal and occipital areas, as compared with the low and less persistent responses from other cortical areas, is worthy of further and more detailed study. The electroencephalograms indicate only that these areas have a marked selective influence on the hypothalamus. They do not indicate whether the influence is by way of direct corticohypothalamic connections or by way of intermediate connections to the hypothalamus by way of other subcortical structures, such as the amygdala, hippocampus, septum, or olfactory region. Such distinction may be resolved by latency studies employing oscilloscopic recording. However, the electroencephalograms strongly suggest that the temporal and occipital areas in the cat exert a more direct and prominent ictal influence on the hypothalamus than do other areas of the dorsolateral cerebral cortex.

DISCUSSION

The anatomic mechanisms underlying grand mal and petit mal epilepsy have received much study. Knowledge of their existence and elucidation has resulted in a better understanding of this disease, which, until a few decades ago, was attributed to unseen powers and therefore labeled sacred.

According to Penfield, Jasper, and McNaughton,[12] the disturbance of epilepsy can affect motor, sensory, autonomic, and psychologic behavior, and, whereas clear-cut clinical types can occur, often the various distinct manifestations may occur together in the same epileptic attack. Just as in the Jacksonian type of motor seizure, spread from one region of the precentral gyrus to another may occur to implicate the entire motor system, so also there may be spread from one cerebral system to another depending on the strength and duration of the irritating agent. Thus, a seizure beginning as petit mal and involving initially the thalamointralaminar system may become grand mal in character by spread to the motor cortex. In nearly all types and combinations of epileptic activity the autonomic system is usually involved in one way or another.

If, therefore, in motor, sensory, and petit mal types of epilepsy each has its own underlying cerebral mechanism, there is no reason to believe that purely autonomic, emotional, or psychologic disturbances should not also have unlerlying cerebral mechanisms. Indeed, cerebral mechanisms underlying emotion have been proposed by Papez[13] and others. MacLean,[14] Schreiner,[9] Lieberson,[15] and Kaada,[16] by ablation or stimulation of discrete portions of the system originally described by Papez, have shown a clearer delineation of those regions of the brain related to behavior, emotional patterns, and autonomic function. Temporal, frontal, and limbic regions are the key foci for such activity and, although their anatomic projection to the hypothalamus has in many cases been demonstrated,[7,17–22] their mutual interrelationship in spontaneous epileptoid activity has not been dealt with experimentally.

Kaada[23] produced autonomic effects from stimulation of rhinencephalic structures. Hippocampal stimulation resulted in ictal activity of the mammillary body,[24] and recently hypothalamic epileptoid activity has been recorded following stimulation of the hippocampus and gyrus cinguli.[25] Besides these effects, we have found little material concerning the spontaneous behavior of the hypothalamus in response to stimulation of higher autonomic structures. It has been shown by Spiegel and Hunsicker[26] and Wall[27] that there are other autonomic cerebral outflows to the lower brainstem which bypass the hypothalamus, but these are probably for localized or special effects. The hypothalamus is by far the most important center for autonomic cerebral outflow, precipitating sympathetic and parasympathetic effects *en masse*,[6]

and these are most likely the autonomic concomitants of such diverse emotional states as love, hate, fear, and anger,[28] each of which has its own set of distinctive bodily manifestations.

The present work shows that the hypothalamus participates immediately and probably directly in the electrically-induced, spontaneous, epileptoid activity of subcortical rhinencephalic structures and of certain cortical areas of the temporal and occipital regions. The hypothalamus can ultimately participate in epileptoid activity of cortical areas outside the temporal and occipital regions, but only when the irritating stimulus is of such excessive voltage and duration as to cause spread to the temporal and occipital areas.

We do not know the extent to which other regions besides the hypothalamus participate in seizure activity originating in subcortical rhinencephalic areas, but the works of Kaada,[23] Green,[24] and Gloor[1] indicate that they do so participate. It is possible, however, that the rhinencephalo-hypothalamic and the temporo-occipito-hypothalamic mechanisms described herein can, under controlled stimulation, be made to operate independently of motor, sensory, and associational somatic systems and, as such, are undoubtedly part of the mechanism for autonomic epilepsy. At the same time, and aside from clinical epilepsy, is the consideration of these mechanisms as a basis for neurotic and psychotic behavior. Emotions such as fear, anger, apathy, or libido, each with its own distinctive autonomic discharge to lower centers, may be excessive in proportion to an external stimulus. They may even be present in the absence of external motivation. In such cases the hypothalamus itself may be irritated by traumatic, vascular, or neoplastic pressures or by altered local chemical factors. On the other hand, similar excessive hypothalamic discharge could just as well be traced to irritation of particular cortical and rhinencephalic structures, which, as we have shown, can so profoundly affect the electrical activity of the hypothalamus.

SUMMARY

1. Hypothalamic seizure activity can be elicited by stimulation of amygdala, hippocampus, hippocampal gyrus, septum, and basal olfactory structures. The ventromedial nucleus is a prominent focal area of the hypothalamus for reception of "epileptic" impulses from the above structures. Stimulation at the same parameter of the ventral and of the dorsal portions of the hippocampus affected different parts of the hypothalamus. The hippocampal gyrus appears to by-pass the hippocampus in its projection to the hypothalamus. Stimulation of the posterior portion of the lateral amygdaloid nucleus produces longer seizure activity in the hypothalamus than do anterior portions of this nucleus. Results indicate that the amygdala affects the ventromedial hypothalamus directly and the mammillary body indirectly through the hippocampus. For reasons unaccounted for repeated constant stimulations of the same structure may result in seizures of varying character in the hypothalamus.

2. Stimulation of the dorsolateral isocortex at a constant, critical parameter showed that not all areas were epileptogenic for the hypothalamus. The most effective cortical epileptogenic areas were found in the temporal and occipital regions. Areas outside the temporal and occipital isocortex became epileptogenic with respect to the hypothalamus when stimulated at high voltage and long duration, and only after spread to temporal areas had occurred.

3. Some clinical implications relative to autonomic and psychomotor epilepsy and emotional states are discussed.

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■ We must note in slight fits movements of chewing or tasting, swallowing, vomiting, and writhing movements of the arms during arrest of respiration. I do not believe that these movements result directly from the epileptic discharge, holding that *such* a discharge, so far as it spreads, puts an end to all movements properly so called, "runs them up" into convulsion. I suggest that an important eye-symptom at, or near to, the onset of some epileptic fits, the apparent alteration in size or distance of external objects, is, on the physical side, a phenomenon of the same order as the chewing movements; that both are the indirect (reflex) results of epileptic discharges of sensory elements. Ferrier produced, by faradising a monkey's "taste centre," movements like chewing and tasting movements some epileptics or their friends describe. It is exceedingly important to distinguish movements proper from convulsion, which is a contention of many movements. I suppose everyone would believe that spitting, rubbing one hand with the other, clutching at the throat (in rapid suffocation?) in slight seizures, are movements too elaborate to result directly from *such* a discharge as that which produces convulsion.

J. Hughlings Jackson in *Ophthalmolgy and Diseases of the Nervous System*, published in 1886.

Treatment of Bell's Palsy

L. B. W. Jongkees, M.D.

FOR MANY YEARS surgical treatment of facial paralysis has given us the opportunity to inspect the diseased facial nerve. The work of Ballance and Duel,[1] Bunnell,[2–4] and many others has made us familiar with the aspect of the nerve traumatized by an injury of the head, damaged by the instruments of an ear surgeon, eaten by an otitis, or destroyed by a tumor. The diagnosis of facial palsy due to these causes is not very difficult and the opinion about their origin does not lead to great controversy.

But there is another group, and an important one too, where the cause is not apparent at all; the paralysis which does not follow an operation or a trauma of the head, where no tumor and no otitis can be found, where no herpetic eruptions are present, and which does not seem to be the sequela of poliomyelitis; the palsy which begins abruptly without any apparent cause, often, but not always, accompanied by pains deep in the ear, the facial paralysis à frigore, rheumatic palsy, Bell's palsy. It is not the disease described in 1829 by Sir Charles Bell,[5] who gave a perfect description of the motor function of the facial nerve but did not describe the disease that now bears his name.

The diagnosis of Bell's palsy is a diagnosis by elimination and there is hardly any unanimity, either about its origin or about its treatment. More unanimity is possible, however, as the histopathology of Bell's palsy is better known and as the results of conservative and surgical treatment can be better predicted.

Inspection of the diseased nerve in early cases of Bell's palsy has taught us that the pathology of this disease can always, or at least in the greatest majority of cases, be found in the vertical part of the nerve in between the bend at the posterior end of the horizontal semicircular canal and the stylomastoid foramen. The nerve is found to be red and swollen, with the trunk very tightly constricted by the nerve sheath and the bony fallopian canal. Often tiny hemorrhagic streaks are found and sometimes even a reddish fluid is seen in the mastoid cells alongside the fallopian canal.[6–12] This is the common finding in cases not older than two to three months' standing. The redness disappears and swelling diminishes in older cases, and cases of very long standing sometimes show pronounced atrophy, the size of the nerve sometimes being no more than that of a silk thread.

The number of histologic examinations of facial nerves in cases of Bell's palsy is not large, as can be readily understood, since people do not die from this disease. Nevertheless, some studies have been reported.

Minkowski[13] was the first to describe the condition of the nerve in a patient whose diagnosis seems to have been carefully made. Eight weeks after onset of the paralysis, the nerve proved to be quite normal from its nuclei downward to the ganglion geniculi, which was also normal. The nerve trunk in the most external part of the fallopian canal showed a strong degeneration. The axis cylinders were mostly intact, however, but the medullary sheaths were found to be greatly swollen. At the point of departure of the chorda tympani and in the stapedius nerve, the fibers were degenerated, too.

Déjérine and his school have given the description of quite a number of histologically controlled cases.[14–16] Some of them are not very convincing for the diagnosis of Bell's palsy, but others seem to be real and unmistakable cases of this disease. The most pronounced deviations have been found in the facial trunk between the stylomastoid foramen and the chorda tympani. Here axis cylinders have disappeared, while those remaining are irregular, hypertrophic, varicose, and coiled up. The axis cylinders reappear toward the center but they show a swelling. Thomas[16] stated explicitly: "Nowhere traces of a perineuritis or an endoneuritis are found," and though most authors use the word neuritis, signs of an inflammation are not given but only signs of degeneration (degenerative disappearance of axis cylinders, myelin found in globules, and so on). Even increase of inflammation cells is never mentioned. Kettel[10] described a piece of diseased nerve and its sheath in a long standing case: "The connective tissue is the seat of edema and hemorrhage and is covered on the inside with remnants of a fibrinous exudate. The nerve filaments are of unequal size and not always of a regularly circular shape in transverse section."

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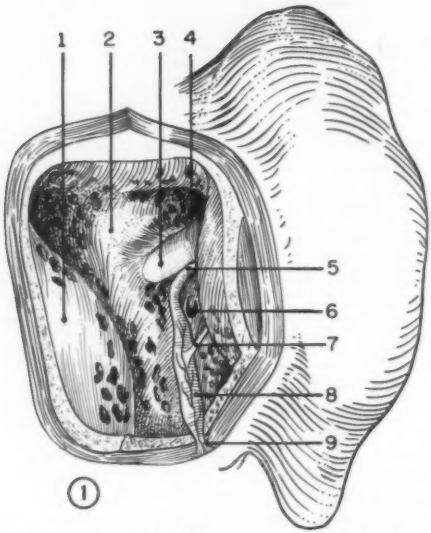

FIG. 1. Aspect of the facial nerve in a patient with acute Bell's palsy. The swelling in the vertical part, widened vessels on its surface, and the narrowing in the stylomastoid foramen are clearly visible. The difference in color between the fiercely red diseased part and the more yellow normal part at the most external knee of the nerve cannot be shown in a black and white drawing. 1. Transversal sinus, 2. mastoid cavity, 3. horizontal canal, 4. aditus ad antrum, 5. horizontal part of facial nerve, 6. opening into middle ear, 7. chorda tympani, 8. swollen part of facial nerve, 9. opened foramen stylomastoideum.

The author himself[36] has had the opportunity to examine a biopsy of a diseased nerve in a very early case of Bell's palsy. A woman with a total facial paralysis of 12 days' standing had distressing pains deep in the ear, which itself proved to be normal. At operation, performed at the request of the neurologist who thought the prognosis was poor and of the patient who could not stand the pain, we found the "normal" pathology, described earlier in this paper: a strongly swollen, fiercely red nerve. The swelling was found to be limited to the vertical segment inside the fallopian canal. The chorda tympani was also swollen and red. When the sheath of the nerve was split open, the nerve burst out of it and it was evident that the nerve had been tightly constricted inside its sheath. A small piece of the chorda tympani was taken for histologic examination by the pathologist, who stated: "This tissue is a small nerve. No sign of inflammation can be found anywhere. Nor is there an increase in the number of cells. The nerve fibers are distinctly, at least locally, degenerated. The myelin sheaths are very strongly swollen. The axis cylinders lying in this preparation show sections of different dimensions. We have to call this a nerve degeneration."

Pieces of nerve sheath in this case and in some others gave normal histologic findings.

The swollen aspect of the facial nerve, without any inflammation to provoke the swelling, had led to the theory that the lesion was probably due to compression, a view which is supported by the findings of Brain, Wright, and Wilkinson.[17] These investigators examined the nervus medianus where it passes underneath the transverse carpal ligament in cases of trauma in this region, causing a paralysis of the median nerve. Here also the compression is accompanied by proximal swelling through edema. Sullivan and Smith[18] examined the influence of cold applied to the shaven face and the result of compression by a circular suture on the facial nerve of rats, and Weiss[19] was able to demonstrate in rats and chickens that chronic constriction of a nerve causes the accumulation of "a fairly large amount of fluid in the endoneural spaces at the central side of this bottleneck."

It is tempting to say here: same causes, same results. But why and how did the compression arise? Since the papers of Hilger,[9] a vascular

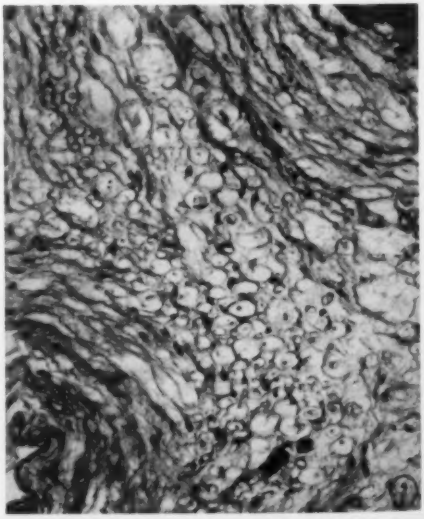

FIG. 2. Chorda tympani in a patient with Bell's palsy of 12 days' duration. There is no sign of inflammation, the nerve fibers are degenerated, the myelin sheaths are very strongly swollen, and the axis cylinders show sections of different dimensions.

origin seems to be very probable. According to his view, defended strongly by Godin,[20] the cause of Bell's palsy is to be sought in a spasm of the exocranial branches of the external carotid artery. The vasa nutritiva (the petrosal artery and the stylomastoid artery) of the facial nerve belong to the domain of the external carotid artery. This vasoconstriction provokes not only an ischemia of the nerve but also gives rise to a change of the condition of the capillary walls. They are damaged by anoxia. Through this change, leading to a capillary hyperpermeability, an abnormal transudation of the blood fluids takes place, from which edema is the result.

The edema compresses the nerve, causing a new obstruction of the lymphatic and venous circulation, leading to a stronger edema. And in this way the vicious circle is closed.

In view of this thesis, the appropriate treatment has to be directed against the vicious circle of edema and compression and therefore against the original vascular spasm. The treatment of choice, especially in the beginning, is a treatment causing vasodilatation; it has to begin energetically and without delay. Heat, produced by special dressings, hot water bottles, infrared irradiation, ultrashort or ultrasonic waves, is one of the most easily attainable ways to provoke vasodilatation. Other methods can be used, too: chemical substances like nicotinic acid, nitrites, and nitroglycerine, blocking the stellate ganglion with novocain injections, or perivascular infiltration around the arteries of the head (temporal, facial, and mastoideal).[20]

It seems to be of special importance to utilize this type of treatment, because therapy with electrical stimulation of the nerve and the muscles of the face plus aspirin in large doses seems to have no effect at all upon the prognosis of Bell's palsy. In extensive statistics Verjaal[21] compared the results in a group of 78 patients treated along the above mentioned lines with those of 31 patients not receiving any treatment. In both groups the percentage of recovery, judged according to the same standards, was identical (67 per cent and 68 per cent). Taverner[22] came to the same conclusion that the older treatment does not influence the healing percentage of Bell's palsy and that about one-fourth of the patients do not recover sufficiently.

From personal communication with neurologists using the vasodilatory treatment, it appears that a greater percentage of recovery is possible and from personal experience the author holds the same opinion. Extensive statistics on this matter have not yet been published. Nevertheless, quite a large number of patients never recover from a rheumatic facial palsy if treated by conservative means only.

On the other hand, Tumarkin[23] rightly stated: "We are tantalized by the feeling that, if only we could have operated the first few days of their illness, we could certainly have saved the patients. But supposing we do see those cases in the first few days of their paralysis how dare we advise operation, when we know that any given patient has a four to one chance of spontaneous recovery." And Smith:[24] "It is said that 75 per cent of cases of Bell's palsy recover spontaneously and therein, we think, lies the cause of lifelong disfigurement for many people."

All those who have operated upon the facial nerve in early cases of Bell's palsy have seen the sometimes surprisingly quick restoration of function, the almost immediate relief of the pain which not so seldom accompanies severe cases, and the nearly constant pathologic picture shown by the diseased nerve at this period.[1,6,10–12,25–31] It is strange to note how many neurologists are theoretically opposed to this operation. They claim that in many cases of Bell's palsy deviations in lacrimal secretion are found, which prove an affection of the nerve proximal of the geniculate ganglion[21,22] which is unattainable at an operation. Or they state that in cases of inflammation decompression can never cure the neuritis or its result, the paralysis.

That no inflammation is present has been expounded in this paper. The proof of a nerve affection unattainable at operation is not very strong either. "Such text book criteria as examination of taste and what the Americans call tearing, i. e., alteration of lacrimal secretion, were seldom of practical value," according to Collier.[32] "Erb's scheme, notwithstanding its ingenious designs, is useless in practice" stated Biemond,[33] and later "the inconstant character of hemiageusy in cases of facial paralysis has to be pointed out."

Crosby[34] stated that in embryological development some fibers of the glossopharyngeal nerve may be drawn forward in the tongue and serve to conduct gustatory impulses when the function of the chorda tympani is destroyed.

But even if the conclusions drawn from the scheme of Erb are valuable, deviations in lacrimal secretion are only found in a small minority of cases (Verjaal,[21] eight times in 82

patients with Bell's palsy; Jacobs and Colony[35] did not mention one case in 44 patients; Jongkees[36–38] none in 15 patients). It seems to be general opinion that, in patients who do not show a clear improvement of facial function within six weeks after the onset of the paralysis, the chance of complete recovery is very small. Incomplete paralysis as a rule recovers spontaneously, but in cases of complete palsy Kettel[11] never saw spontaneous recovery which had not begun within one month.

If the faradic reaction becomes negative in cases of complete paralysis, many think this is an extra bad prognostic sign, and the same holds true when electromyography shows "fibrillation." Patients complaining about severe pain at the onset of the palsy and those having spontaneous complaints about disturbed taste at the homolateral side of the tongue have hardly a chance of spontaneous recovery. And in cases of recidivism prognosis is very bad, too.

Park and Watkins[39] found that normal electrical reactions indicate an excellent prognosis: complete healing within six weeks in all their patients. Partial degeneration indicated by the electrical reactions led to restoration of the facial function in 87 per cent of the cases in from one to six months, and of the patients with a complete electrical degeneration reaction only 57 per cent improved. Though the author is a devoted supporter of conservative treatment, I agree with Bergström,[40] Cawthorne,[6] and Kettel,[11] that a patient with a total Bell's palsy, showing no improvement after two months, should be submitted to a decompression. Also those nerves showing an increasing paresis or a recidivation should be decompressed. Finally, in those patients complaining about severe pain deep in the ear, of loss of taste especially when the electrical reactions of nerves or muscles show degeneration, an operation may be indicated much earlier.

The operation itself is simple and not mutilating. Hospitalization for about five days is adequate.

The effect of the operation is more amazing in early cases. In the author's series all ten patients operated upon within three months after the onset of the disease showed a remarkably quick reappearance of the first signs of function, and the end result was generally total recovery. Five patients had the palsy for more than three months; four were improved by the operation but a paresis remained. At rest the face was symmetric, however, and

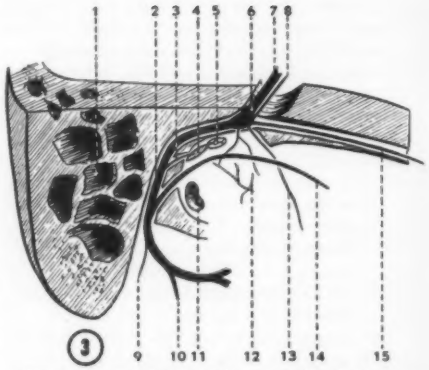

FIG. 3. Course of the facial nerve inside the temporal bone. 1. Mastoid cells, 2. facial nerve in fallopian canal, 3. stapedial nerve, 4. stapedial muscle, 5. stapes, 6. ganglion geniculi, 7. facial nerve in internal porus, 8. nervus intermedius Wrisbergi, 9. posterior auricular nerve, 10. nervi stylohyoides and digastricus, 11. round window, 12. plexus tympanicus, 13. nervus petrosus superficialis externus, 14. chorda tympani, 15. nervus petrosus superfacialis major. From this drawing, Erb's scheme may be read immediately. Bell's palsy pathology has been found in all cases of this series in the part between the lines numbered 3 and 9.

their eyes could be closed. In one patient no improvement followed the decompression performed four months after the onset. In none of our patients did we find any disturbance of lacrimal secretion which could not be explained by a concomitant conjunctivitis or a lagophthalmos.

In the period of five and one-half years during which 15 patients were operated upon for Bell's palsy, we performed operations upon the facial nerve for paralyses of other origin in more than 100 patients, which may prove that conservative treatment in patients suffering from Bell's palsy is tried as long and as intensively as possible. Conservatism, however, has its limits, because otherwise disfigurement threatens patients who could have been saved easily by an operative procedure. An operation performed within the first two months restores the facial function in almost all patients suffering from Bell's palsy. Postponement of the operation makes the prognosis less and less favorable.

Some leading neurologists are not convinced by the results published by those who performed operative decompression, as the series reported by them are small. They ask for statistical proofs.

Even a small series such as the one given here, however, has statistical value. Treated

TABLE 1

Number	Sex	Age	Duration of Paralysis Before Operation (in months)	Electrical Degeneration Reactions	Paralysis	Result of Operation (more than one year ago)
1.	female	42	24	+	total	improved
2.	male	47	4	+	total	no improvement
3.	female	7	12	?	total	nearly recovered
4.	female	40	3½	+	total	recovered
5.	male	5	5	?	total	improved
6.	female	44	½	+	subtotal	recovered
7.	female	35	2½	+	total	recovered
8.	female	36	3	+	total	recovered
9.	male	53	3	+	total	nearly recovered
10.	female	40	1½	+	total	recovered
11.	male	59	2	+	total	recovered
12.	female	51	2	+	total	recovered
13.	female	38	3	+	subtotal	nearly recovered
14.	female	27	1½	+	subtotal	much improved
15.	male	61	2	+	total	recovered

conservatively, the patient who shows no trace of improvement and total electrical degeneration after more than six weeks has an extremely small chance to recover,[11,39] perhaps 5 per cent. In the series given here 14 out of 15 patients recovered more (nine) or less (five) completely. Statistics teach us that the chance of coincidence is only one in 10.[15] Therefore, the results are highly significant. Nevertheless, some are opposed to a new treatment, raise theoretical but unproved objections, and do not offer patients the best chance of recovery. In my opinion, patients suffering from Bell's palsy should be treated as serious cases from the beginning. They should be kept in their room or in bed to avoid drafts and cold. The application of heat and salicylates is advisable. After about three weeks the electrical responses of nerve and muscles should be examined. If a total electrical degeneration reaction is found and if the paralysis remains complete, the prognosis is dubious. If after a further daily electrical and general treatment at a maximum of six weeks the circumstances remain unchanged in these cases, operative treatment should be advised.

SUMMARY

Bell's palsy is the consequence of an arteriolar spasm of the nutrient vessels of the facial nerve. Histologic examination does not show any trace of inflammation, but only of degeneration provoked by compression and edema. Conservative treatment should be directed against the arteriolar spasm and must, therefore, pursue vasodilatation of the feeding arteries. It should be started as soon as possible. In a not very small percentage of the cases, however, conservative treatment does not lead to recovery. By an operative decompression of the diseased nerve, the function of the paralyzed nerve can be restored in quite a large group of these patients if not postponed too long. The duration of the palsy is of primary importance for the prognosis. The indications for the operation are discussed.

The author wishes to thank Professor Biemond, neurological department, University of Amsterdam, for his kind interest in the problem of Bell's palsy and for his critical reading of this paper.

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■ Just as palsy depends on destruction of nerve tissue in a motor centre, *however produced*, so disorderly "activity" of muscles depends on instability, however produced, and my opinion merely is that embolism is the *most frequent* cause of the local instability allowing choreal movements. Similarly we may, in cases of defect of intellectual expression (aphasia), without implying an actual separation, arrange the cases for study in two distinct lines departing from health: (1) degrees from defect of articulating power to speechlessness, owing to different quantities of nerve tissue *destroyed;* and (2) degrees of disordered succession of movements producing slight difficulty of articulation, or unintelligibility, or, in a higher range of evolution and association of movement and sensation, mistakes in words and incoherence. It will, I think, be found that the first class is usually caused by clot, which destroys, and the second by embolism, which may lead only to ill-nutrition. The two kinds of defects, however, are by no means altogether separate even in cases of embolism; with hemi-chorea there is probably always some paralysis.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System*, published in 1868.

The Electroencephalogram in Microcephaly

Alberto Fois, M.D. and Carl M. Rosenberg, M.D.*

THE PURPOSE of the present investigation was to survey a group of microcephalic children from a large state hospital in order to determine what electroencephalographic abnormalities are found in this group and the extent to which they are specific for microcephaly.

MATERIAL AND METHOD

A group of 22 patients with severe degrees of microcephaly were selected from a large population of mentally retarded patients. The age range was from one to 17 years; 14 were male and eight female.

In every case a recording was made in both the waking and sleeping states with a Grass eight-channel electroencephalograph. Solder disk electrodes were placed in the frontal, temporal, parietal, and occipital areas over both hemispheres. Contact with the scalp was made through bentonite electrode paste, and the electrodes were fastened to the scalp with collodion. All recordings were monopolar. One or both ears were usually used as a reference, though in some cases a reference electrode was placed on the chin or over the low occipital area.

RESULTS

The electroencephalographic classification of these cases is shown in table 1. A history of clinical seizures occurred in five patients (22 per cent); four of these showed seizure activity in their electroencephalograms. Among the 17 patients without a history of seizures, spike seizure discharges were obtained in ten. As in other types of cases, seizure activity was more common in the sleeping than in the waking state.[1] The types of seizure discharge were as follows: petit mal, three cases; hypsarrhythmia, one case; 14 and 6 per second positive spikes, one case; mixed type of seizure discharge, two cases. Focal seizure activity was limited to the frontal areas in one case, the occipital area in one, and the parietal area in two. In one case it involved an entire hemisphere. Background activity in the waking state was normal in six cases, slightly fast in five, and very fast in one. It was slightly slow in two cases and exceedingly slow in three cases. Mixed fast and slow frequencies occurred in five cases. An asymmetry was present in three cases.

Abnormalities of sleep patterns were frequent. Biparietal humps were absent in nine cases. Spindles were absent in 12 cases. The most characteristic finding was a diffuse reduction in the voltage of all areas in both the waking and sleeping states (figure 1); this occurred in 14 cases (63 per cent).

COMMENT

The high incidence of seizure activity in this group is not surprising in view of the fact that 22 per cent had clinical seizures. Fast or slow activity, which occurred in 58 per cent of cases, is found in a great variety of conditions and is to be expected in association with seizure activity.[1] However, exceedingly low voltage activity in children more than six months of age is uncommon, and the occurrence of low voltage electroencephalograms in 63 per cent of these patients with microcephaly is noteworthy.

Exceedingly low voltage or flat electroencephalograms are obtained in conditions where the cortex has been severely damaged or surgically removed.[2] It seems likely that in a high percentage of patients with microcephaly there is some degree of "decortication;" that

TABLE 1

ELECTROENCEPHALOGRAPHIC FINDINGS* IN 22 PATIENTS WITH MICROCEPHALY

E.E.G.	*Number*	*Per cent*
Low voltage awake, poorly patterned asleep	14	63
Normal	6	27
Mixed fast and slow	5	23
Slightly fast (F-1)	5	23
Focal spikes	5	23
Petit mal	3	14
Very slow (S-2)	3	14
Asymmetry	3	14
Slightly slow (S-1)	2	11
Very fast (F-2)	1	5
Hypsarrhythmia	1	5
14 and 6 per second positive spikes	1	5

*Nonexclusive; each patient is listed as having one or more findings. The numbers cannot be added to give the total in the series (22 cases) and the percentages do not add up to 100.

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With the technical assistance of Howard Caton.
This research was aided by a grant from Chicago United Cerebral Palsy.

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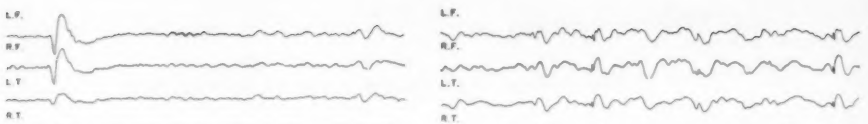

FIG. 1. Microcephalic patient, age seven years. *A.* Awake, eyes closed, relaxed. The low voltage activity shown here is common in patients with microcephaly. The normally high voltage of the blink at the left gives assurance that the generally flat appearance of this recording was not due to high resistance. *B.* Low voltage, unpatterned sleep activity with spikes, common in microcephaly.

is, certain normal cellular elements are nonfunctional or absent. The commoness of abnormal sleep patterns is probably due in part to cortical defects, but in some cases it may reflect disorder in subcortical structures.

SUMMARY AND CONCLUSIONS

Electroencephalograms in both the waking and sleeping states of 22 patients with microcephalus have been recorded and analyzed. Seizure activity occurred in 64 per cent of these patients; 72.7 per cent had fast, slow, or a mixture of fast and slow background activity in the waking electroencephalogram. The most striking finding in this group was a reduction of voltage in the waking and sleeping states and disorganized, poorly-patterned sleep activity. Low voltage activity in both the waking and sleeping state is probably due to a deficiency of functional cortical elements in these patients. The disorganized sleep patterns are probably due in part to cortical deficiency, and are in part a reflection of defective functioning of the subcortical centers.

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■ The result of recent researches has been to establish in the fullest manner the truth of Sir Charles Bell's great discovery, that the posterior roots of the spinal nerves are devoted to sensation only, and the anterior roots to motion only. In one article, at least, the creed of today is the same as that of yesterday: and it is some comfort to have it so, for in many other articles faith is not a little shaken by the changes of belief which are now found to be necessary.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Hematoencephalic Exchange as a Function of Age

Williamina A. Himwich, Ph.D., JoAnn C. Petersen and Mary L. Allen

THE HEMATOENCEPHALIC EXCHANGE is a rate phenomenon which varies with the material exchanged between the blood and the brain. The exceedingly slow passage of some substances into brain has led to the concept of a blood-brain barrier. This term, however, carries the idea of an absolute barrier rather than a differential rate phenomenon. For this reason we have used the term, hematoencephalic exchange.

The change in ease with which materials enter the brain as the animal matures has excited the interest of a number of investigators. In human beings, the relative permeability of the brain of the premature infant to bilirubin has been offered as an explanation for the development of kernicterus in babies with erythroblastosis.[1] Irrespective of the blood level, kernicterus develops rarely, if at all, in the adult human being. The only other data available in the human newborn, however, do not support this thesis. Gröntoft[2] has studied the staining of the brain by dyes injected into the blood stream in human infants who died at, or shortly after, birth and in newborn rabbits. As a result of his work, he believed that some mechanism blocks the free exchange of substances between blood and brain, even in the very young, unless anoxia has injured the brain. However, the babies and animals he studied were dead before injection and the permeability of the brain might have been altered. On the other hand, Behnsen[3] found that trypan blue injected into mice colored the brain more in the young than in the older animals. Stern and Peyrot[4] traced the entrance of sodium ferricyanide from the blood into the brain in the young of several species and found that the substance penetrated into the brain freely until the animals had their eyes open, after which the ferricyanide could not be detected in the brain. Hess[5] has followed the development of the ground substance in the mouse and the guinea pig and has demonstrated that it becomes apparent histologically at about the same time that the brain is no longer stained by in vivo injection of dyes.

Several investigators have studied the entrance of radioactive phosphorus into the developing brain. Fries and Chaikoff[6] showed that more P^{32} entered the brains of newborn rats than of older animals. By the time the animals weighed 50 gm. or were approximately three or four weeks old, the rate of penetration was only slightly greater than in the adult. Bakay[7] and Manukyan[8] have both demonstrated the decreased passage of this tracer element into the brains of rabbits as they mature. They conclude that in this species free exchange does not occur after approximately 30 days of age. The gradual appearance of the relatively impermeability of the brain to certain substances seems to us to be an important facet of the growing brain which might correlate with the attainment of chemical and neurologic maturity. The studies reported here were planned to follow the function of the blood-brain barrier in the rat, using as the criterion the passage of L-glutamic acid from blood to brain. The use of this metabolite was induced by the current interest in this substance in the field of psychiatry.[9]

Glutamic acid not only occurs abundantly combined with other amino acids in brain proteins, but is also present in large amounts in the free form. During the period of rapid growth the young animal needs either to draw large amounts of this amino acid from the blood or to synthesize it rapidly to meet the needs of new nervous tissue. If the brain is capable of removing this material from the blood, that is, if the hematoencephalic exchange is not selective, a high blood level of glutamic acid may be reflected in an increase in free glutamic acid in brain.

METHOD

Four age groups of albino rats were studied: 24 hours old, 10 to 11 days old, 17 days old, and adults (six months old). The two youngest groups were injected intraperitoneally with 2 gm. per kg. of glutamic acid as sodium glutamate, a control sodium chloride solution containing an amount of sodium equivalent to that in the sodium glutamate, or 1.5 gm. per kg. of glutamic acid as ammonium glutamate. The injection of as much ammonium glutamate as sodium glutamate was lethal to most adult

From the Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Illinois.

animals, so a lower level was chosen. The ammonium glutamate was omitted in the 17 day old animals, but they were given sodium glutamate and sodium chloride solutions as described above. Thirty minutes after injection, the animals were decapitated and the brains treated as described below.

In an attempt to stimulate the ingestion of increased glutamic acid in food, the test solutions were administered daily by stomach tube for nine days to male rats averaging six months of age, and weighing between 250 and 300 gm. The animals were fasted approximately eight hours during the day before they received the solutions by stomach tube. They were allowed to eat freely during the night and so maintained their body weight. On the tenth day, after the animals were starved for 24 hours, a final dose of appropriate test solution was given by stomach tube. Thirty minutes later the animals were decapitated and the brains removed.

All solutions administered either by stomach tube or by injection were adjusted to room temperature and to pH 7.0. The glutamate salts were prepared by dissolving L-glutamic acid in water and neutralizing with the appropriate base.

The brains were all analyzed by routine procedures, with certain exceptions dictated by brain size. For the 24-hour and 10-day old groups, several whole brains were combined to obtain samples large enough for analysis; in the 17-day-old group, the brains were cut at the midcollicular level and the area cephalad to the incision used. In the adult rats the same area was studied, but one hemisphere was used for glutamic acid and the other for glutamine analyses. These changes in procedure undoubtedly made for greater variations within the same experimental group, but made possible a number of analyses on the same brains.

In every case after the animal was decapitated, the brain was removed and frozen immediately in dry ice and ether. Less than 15 seconds elapsed between decapitation and complete freezing. The frozen brains were stored in aluminum foil and waxed freezer paper at −22° C. until analyzed. For the analyses, they were weighed while still frozen and homogenized in cold trichloroacetic acid. The method of Prescott and Waelsch,[10] as modified by Himwich and Petersen,[11] was used for glutamic acid. Glutamine was determined by the method of Bessman.[12] Alpha-keto glutaric acid, pyruvic acid, moisture, and total nitrogen were determined by the methods of Friedmann,[13] Graves and Himwich,[14] and Kelley,[15] respectively.

Blood levels of glutamic acid were determined on blood obtained by decapitating the animals and collecting the freely flowing blood.

RESULTS

Data on the control groups of animals for free glutamic acid and glutamine in the brain show that, on a wet weight basis, these substances increase from birth to six months of age (table 1, figure 1). The increase, however, is not at a regular rate. For free glutamic acid the greatest increase occurs between the tenth and seventeeth days, with the brain containing almost the adult amount of this substance at 17 days. For glutamine, on the other hand, there is a definite fall at the tenth and at the seventeenth days, followed by a rise to the adult value. The reaction of glutamic acid + ammonia ⇋ glutamine is readily reversible and probably represents the principal route of detoxication of ammonia. Hence, it seems better to consider in the control animals the increase with age in the total of free glutamic acid plus free glutamine. Even on this basis, however, the increment per day between one and ten days is considerably less than between 10 and 17 days. During the same period of time, that is, birth to 17 days,

TABLE 1

FREE GLUTAMIC ACID AND GLUTAMINE IN RAT BRAIN AFTER ADMINISTRATION OF SODIUM GLUTAMATE OR AMMONIUM GLUTAMATE

	Control	*NaGlut.*[1]	*NH_4Glut.*[2]
24 HR. OLD			
Glutamic acid, mg.%	63.5	79.9**	74.3**
	(15)[3]	(17)	(18)
Glutamine, mg.%	56.8	52.4	46.8
	(16)	(14)	(14)
10 TO 11 DAY OLD			
	Control	*NaGlut.*[1]	*NH_4Glut.*[2]
Glutamic acid, mg.%	94.0	82.9*	76.8**
	(10)	(10)	(14)
Glutamine, mg.%	47.7	39.2**	59.3**
	(15)	(19)	(19)
17 DAY OLD			
	Control	*NaGlut.*[1]	*NH_4Glut.*[2]
Glutamic acid, mg.%	137.9	141.7	
	(10)	(10)	
Glutamine, mg.%	40.3	46.1	
	(10)	(10)	
6 MONTHS OLD			
	Control	*NaGlut.*[1]	*NH_4Glut.*[2]
Glutamic acid, mg.%	146.9	152.9	160.3
	(18)	(17)	(7)
Glutamine, mg.%	71.0	71.3	53.0
	(11)	(19)	(5)

* difference from the control is significant at 5% level.
** difference from the control is significant at 1% level.
[1] 2 gm./kg. glutamic acid as sodium glutamate.
[2] 1.5 gm/kg. glutamic acid as ammonium glutamate.
[3] Numbers in parentheses are number of animals used.

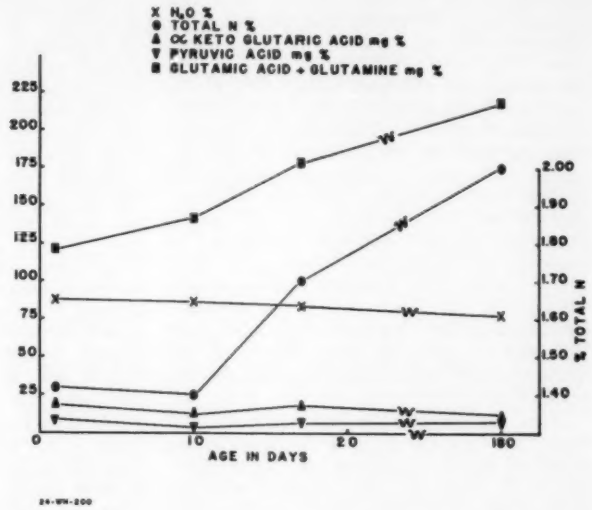

FIG. 1. Water, total nitrogen, alpha-keto-glutaric acid, pyruvic acid, glutamic acid plus glutamine in developing brain.

water is decreasing and total nitrogen is increasing. The values for alpha-keto-glutaric and pyruvic acids have a tendency to remain constant, with the exception of the values for the 10 day old animals which are consistently low (figure 1).

The injection of either sodium or ammonium glutamate increased the free glutamic acid in the brains of the 24 hour old rats. The animals in both of these groups probably convulsed but, due to the inherent motor restlessness of this age group, it is impossible to be certain of the convulsions. The animals at 10 days of age receiving the glutamate salts convulsed about 15 minutes after the injection. Electroencephalograms taken from the cortex revealed large slow waves and some spikes. Glutamic acid was actually lower in these brains than in the controls for that age group. The same is true for both glutamic acid and glutamine in animals receiving sodium glutamate. In the animals given ammonium glutamate a decrease in glutamic acid was offset by the formation of additional glutamine. Since brain metabolism of both these groups of animals can be assumed to be affected by the convulsions and the overall metabolism considerably changed, no attempt was made to follow the sum of glutamic acid and of glutamine.

At 17 days only an occasional animal convulsed when given sodium glutamate. In the groups of adult animals none convulsed. In neither the 17 day old animals nor in the adult animals did the administration of glutamate or glutamine affect the brain level of glutamic acid or of glutamine significantly (table 1).

The blood glutamate was raised in each of the age groups by the administration of glutamate as shown by the average blood levels 178, 166, 210, and 92 mg. per cent at 30 minutes after the administration of sodium glutamate in the newborn, 10 day old, 17 day old, and adult animals, respectively. These rises represent increases of approximately 100 per cent, since the normal blood level is between 1 and 2 mg. per cent.[16] It is difficult in our present state of knowledge to interpret the data on alpha-keto-glutaric acid and pyruvic acid. Only the falls in pyruvic acid and in alpha-keto-glutaric acid for the newborns given glutamate were significant.

DISCUSSION

The control glutamate values obtained in the six months old animals compare favorably with those reported by Schwerin, Bessman, and Waelsch[17] and also with values given by Dawson.[18] The glutamine values reported are slightly higher than those of Waelsch and his colleagues[17] and are comparable to those reported by Dawson[18] and by Tigerman and MacVicar.[19] The sum of these two substances is in the same range as reported by Haber and Saidel.[20] To our knowledge, values are not

available in the literature for the other age groups.* It is interesting that glutamic acid approaches the adult level at 17 days, at which time Tallan reported N-acetyl-L-aspartic acid has attained the maximum value.[22] It is at this time also that postural attitudes attain full development and in the next three days the animals will show the characteristics of adult behavior.[23] The data for alpha-keto-glutaric and pyruvic acids are higher than most values reported[24] but are lower than those of Froman, Orten, and Smith.[25] Although our method of removing and treating the brains made little, if any, difference in glutamic acid and glutamine values, it is quite probable that it caused an increase in such metabolites as pyruvic acid. The total nitrogen and water content of the brains show the expected shifts as the brain develops.[26,27]

When we consider the penetration of glutamic acid from the blood to the brain in the adult, we find no significant increase irrespective of the form in which glutamic acid was given (table 1). These values suggest, as has been indicated by Waelsch and his colleagues,[17] by Dawson,[18] and by Kamin and Handler,[28] that glutamic acid does not enter the brain in the adult animal. Klotzsche[29] and Boulanger, Griffiié, and Osteux,[30] on the other hand, reported experiments which indicate that glutamic acid does penetrate into the brain. The former worker fed glutamic acid, 1.25 gm. per kg., for eight weeks to mice and found an increase in glutamic acid and glutamine resulting in a total value for the two substances of 340 mg. per cent as compared to the normal value of 160 mg. per cent. The latter investigators, using the isolated perfused head of the dog, found a significant uptake of the amino acid from the blood at plasma levels only slightly higher than normal. It is possible that the increases reported by the French workers are due to anoxia, since normal reflexes are lost by their preparation in 45 to 75 minutes. The effect of feeding glutamic acid to mice is similar to the results obtained by Tigerman and MacVicar[19] when an ammonium salt was fed with glutamic acid. These authors unfortunately determined only glutamine in the brain. When they injected approximately 1.7 gm. per kg. of glutamine or of glutamic acid with ammonia 15 minutes before sampling the brain, they obtained increases of brain glutamine only in the case of glutamine injection. Such divergent results suggest that data on the permeability of the brain in the adult animal may be dependent upon variations in the experimental conditions which are not adequately appreciated. In connection with this problem are the interesting experiments of Sacks[31] who has shown that carbon-labeled fumarate is taken from the blood by the brain and rapidly converted to carbon dioxide in man. However, the total quantities of fumarate which entered the brain were very small (0.27 mg. per cent).[32] It is always possible that the level of glutamic acid in the adult brain is maintained at such a constant level that any extra amount of amino acid taken from the blood is rapidly metabolized by being incorporated into protein, decarboxylated to form gamma-aminobutyric acid, or deaminized to alpha-keto-glutaric acid.

The data suggest immediately that free glutamic acid enters the brain easily in the 24 hour old animal, but does not penetrate readily at other age levels. In the 24 hour old animal there apparently is no advantage to the administration of glutamic acid, either as the sodium salt or as the ammonium salt. It must be remembered, however, that only three-fourths as much glutamic acid was given in ammonium glutamate as when sodium glutamate was injected. Larger quantities of ammonium glutamate resulted in marked convulsions in the adult animal, due probably to the ammonium ion. In the 17 day old animal it is also apparent that glutamic acid does not enter the brain readily. The occasional animal that convulsed probably represented the exception.

The situation in respect to the 10 day old rat is much more difficult to interpret. Animals of this age given either sodium or ammonium glutamate show convulsive seizures about 15 minutes after the injection. Large dysrhythmic electroencephalographic waves may be obtained from cortex during this time. These waves are similar to those reported by Druckman and Chao[33] in very young children with convulsions. In attempting to interpret these data it is important to keep in mind the state of the brain in the rat at 10 to 11 days of age. It has been shown by Koch and Koch[34] and others[35] that it is at this age level that the animal first begins to lay down large quantities of protein and phospholipid. The change in water content for instance between the tenth and seventeenth days is more rapid than at any other period after birth. It is at 10 days that Crain[36] first was able to obtain spontaneous electrical activity from the cortex, and Su-

*These values supersede those given by Himwich and Himwich,[21] since a systematic error was found in the calculation of those data.

gita[37] found that thickness and volume of neurons in the cortex approached the adult level. Gollan[38] reports that at this age the rat loses its infantile reaction to hypothermia. Active mitosis is still occurring in the neuroglia.[39] Many enzymes, such as glutamic acid dicarboxylase, are increasing at a rapid rate.[40] It seems quite probable that we have not been able to catch the entering glutamic acid before it has been metabolized in these animals. We have a hint as to what may happen when we consider the increase in glutamine following the injection of ammonium glutamate. It is conceivable that in this group of animals the additional ammonium is removed by glutamic acid to form glutamine.

The development of convulsions may be due to the fact that glutamic acid entered the brain. Since convulsions occurred as frequently in those given sodium glutamate as in those with ammonium glutamate, we feel justified in assuming that the seizures were due to the glutamate ion and not to the ammonium ion. The whole picture, however, is complicated by the fact that Gellhorn and Ballin[41] have shown that susceptibility to convulsions induced by electrical stimulation varies with age, younger animals convulsing more readily than older animals. It is difficult to reconcile occurrence of convulsions in the 10 day old animals with the beneficial effects of the administration of glutamic acid reported in petit mal epilepsy[42] and in audiogenic seizures in mice.[43] The results reported in these cases, as well as the increases in well-being reported in aged patients,[9] may very well not be related to the penetration of glutamic acid into the brain but to some other mechanism. These questions still await elucidation. Kittens up to the age of five or six months vomit but do not convulse after the injection of sodium glutamate, while adult cats do not vomit.[16] The observation suggests that glutamic acid may enter the brain more readily in kittens than adult cats. We have not noted convulsions even in four week old kittens. The effect of the convulsion would undoubtedly be to accelerate metabolism, and glutamate might well be used by the brain for its metabolic needs if not enough glucose were present.

Another problem which must be assessed in evaluating these data is the hyperglycemic effect of glutamate in rats,[44] as well as in other animals.[45] Although the exact mechanism of this hyperglycemia is not clear, most investigators agree that there is a mobilization of liver glycogen. Blood sugars were not determined on the rats, but it would seem probable that only in the adult rats would there be enough reserve of liver glycogen to permit a significant hyperglycemia. Undoubtedly, the results in adult animals are complicated by a rise in blood sugar which might increase the movement of glucose into the brain and conceivably block the entrance of glutamate. Dyes have been shown by Aird and his colleagues to block the entrance of cocaine into the brain of the cat.[46]

SUMMARY

The relation between the changes in glutamic acid, glutamine, pyruvic acid, alpha-keto-glutaric acid, water, and total nitrogen in the developing brain of the rat and the development of behavioral patterns are discussed. Hematoencephalic exchange of glutamic acid is relatively fast in the newborn rat, as shown by increases in glutamic acid in brain when the blood level of this amino acid is raised. In the adult animal under similar circumstances the exchange cannot be detected by the methods used in this study.

We wish to thank Carol Stewart for the nitrogen determinations and Juanita Graves for the moisture analyses.

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Peripheral Nerve Tumors as a Cause of Pain in the Lower Extremities

Sidney W. Gross, M.D. and Aaron Schwartz, M.D.

NEOPLASMS of the peripheral nervous system are uncommon. The diagnosis and treatment of an uncommon disorder or disease are often looked upon as lacking in general interest except to the specialist in that field. This is an unfortunate attitude, since a rare disorder which can be cured or improved deserves as much attention as the more common diseases.

Recently four elderly patients with constant severe lower extremity pain came under our care. They all had endured considerable pain prior to definitive diagnosis and treatment. In all four patients benign solitary peripheral nerve tumors were found which were surgically excised, with relief of pain.

That peripheral nerve tumors should be thought of in the differential diagnosis of lower extremity pain is seemingly quite obvious, yet diagnosis is frequently missed. The vital point in making the diagnosis is a thorough physical examination of the extremity, including primarily careful palpation in various positions.

Benign solitary peripheral nerve tumors have been studied extensively in the past. The series of Lewis and Hart[1] reported from the Johns Hopkins Hospital in 1930 consisted of 11 such tumors. Since then several series of these tumors have been presented by various investigators. Cutler and Gross[2] reported 25 new cases in 1936. Stout[3] reported 194 previously published cases, plus 50 additional new ones in 1935.

The term "neuroma" was introduced into medical literature by Odier in 1803. It was applied by him to tumors formed by the diseased enlargements of nerves. In 1829 William Wood of Edinburgh published the records of 29 cases of neuromas he had collected from various sources. He believed that they developed from the connective tissue of the nerves and not from the nerve fibers themselves.

The common neuroma developing at the proximal cut end of a nerve following trauma or surgery is a hyperplasia and not a true neoplasm. The most common solitary tumor found on a peripheral nerve is a perineural fibroblastoma. There has been considerable discussion concerning the origin of these tumors. Whether the isolated growth takes origin from the neurilemmal sheath of Schwann, perineurium, or epineurium has been studied and debated by many authorities. Penfield,[4] agreeing with Mallory, held these tumors to be of mesodermal origin, derived from the perineural sheath; therefore, he used the term "perineural fibroblastoma." Although many pathologists today believe that these tumors arise from the neurilemma cells of Schwann and are, therefore, of ecodermal origin, Tarlov[5] has presented convincing evidence that this type of cell presents the morphologic characteristics of the fibroblasts. Moreover, the fibroblastic nature of perineural fibroblastomas seems evident on the basis of the rich reticulum stroma, similar to that of the endoneurium. Using special staining technics for the demonstration of Schwann cells, Tarlov was never able to demonstrate such cells in any of 12 perineural fibroblastomas examined. Because of the lack of agreement concerning the origin of nerve sheath tumors, many names have been applied to them, such as, "neurofibroma," "neurinoma," "Schwannoma," "neuroma," "fibroma of nerve sheath," and others. The issue is often evaded by using the nonspecific term, "nerve sheath tumor."

On microscopic examination these tumors present long spindle cells arranged in parallel rows. The nuclei often form palisades. Spindle shaped cells are also seen in interlacing bundles and whorls. The cells may deposit little or no intercellular substance. Degenerative changes are common, with loss of cell structure, accumulation of interstitial fluid, and myxomatous changes. There are areas of high cellularity and low cellularity. Large phagocytic cells are sometimes seen in areas of cystic degeneration. Mitoses are seen rarely.

Tumors of peripheral nerves may be the site of local pain which radiates along the course of the nerve. On palpation, they are round, smooth, well demarcated, and movable from side to side but not movable in the long axis of the nerve. In our cases the tumors have been tender to palpation. Comparison with palpatory findings in the contralateral limb is helpful when small tumors are suspected. Our cases occurred in elderly patients whose pain remained undiagnosed after seeking medical attention for periods varying from two months

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to five years. The pain produced by these tumors was fairly constant and not alleviated by rest, heat, or cold. There may be no sensory or motor deficits when the tumor is benign.

The treatment of these tumors is surgical removal. Perineural fibroblastomas grow in such a way as to push the nerve trunk to one side or to expand the nerve trunk about the tumor. The nerve proper does not enter the mass, but is displaced laterally or completely surrounds the mass, so that a good cleavage plane is frequently found and the functional integrity of the nerve is unaltered. In those cases where a good cleavage plane is present, the tumor may be enucleated without resection of the nerve trunk. Where there is any question of malignancy or in the absence of a good cleavage plane, resection should also be carried out. The loss of nerve length after a resection can be overcome by proper positioning of the extremity, mobilization of the proximal and distal nerve ends, the normal elasticity of nerve, and rerouting of the nerve.

In two of our cases presented here, the tumor and nerve trunk were resected and a primary end-to-end suture done.

Case 1. A 63 year old white male had severe pain in the right calf radiating to the plantar surface of the right foot of five years' duration. The patient had been seen by many physicians during this period. In June 1950 he was operated upon and several nerves in the right foot were severed, with no relief of pain. He was reoperated in October 1950 and again the pain persisted. He was first seen by us in March 1952, with the same symptoms. The patient had also noted that any pressure on the right calf caused shooting pains radiating to the plantar surface of the right foot.

A surgical scar was revealed on the sole of the right foot. There was no evidence of vascular insufficiency. Both dorsalis pedis arteries were easily palpable. There was no impairment of straight leg raising. No sensory changes or abnormal reflexes were elicited. Palpation of the foot did not cause any pain. Palpation in the calf, approximately 10 cm. below the popliteal fossa, caused the patient to complain of pain in the foot and calf. A tender mass was palpated in this area. The clinical impression was a tumor of the tibial nerve.

The patient was operated upon under general anesthesia and a tumor of the tibial nerve was found. This tumor was 4 by 3 cm. in size. The tumor was resected with 5 mm. of uninvolved nerve on both ends of the specimen. This defect was overcome by mobilization of the tibial nerve distally and proximally. Nerve suture was done with fine silk. The defect was further corrected by immobilization of the knee joint in a plaster of paris cast at an angle of 110°. The postoperative course was uneventful, though he continued to have pain for the next several weeks. This gradually subsided. In a recent note (1956) he reported complete freedom from pain.

Pathologic report. The specimen consisted of a roughly globular mass of tissue, weighing approximately 8 gm. and measuring 3 cm. in diameter. The mass was completely encapsulated except for opposite poles, at which sites peripheral nerves appeared to be passing. On section the tumor was seen to be a mottled orange-yellow and grey color.

Microscopic examination revealed a moderately cellular, moderately vascular neoplasm which contained areas of greater and lesser cellularity (figure 1). The cells were elongated, with indefinite cytoplasmic outlines and ovoid to elongated nuclei. These tended to be arranged in parallel rows. In the denser areas the nuclei of the cells tended to arrange themselves laterally in parallel formations, leaving a clear cytoplasmic zone between them. The cells in the less dense areas appeared to be essentially similar but presented a loose-meshed reticular background. Small groups of lymphocytes were present. The entire tumor was surounded by a well formed collagenous capsule. Diagnosis: Perineural fibroblastoma.

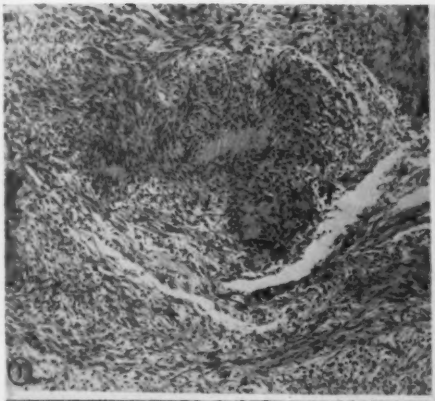
Case 2. A 77 year old white female developed herpes zoster in July 1954, involving the lateral plantar area of the right foot and the lateral aspect of the right calf. This pain was associated with the typical herpetic eruption. Following the disappearance of the eruption, the pain in the calf and foot persisted and was constant and severe, requiring Demerol and morphine for relief. The patient was seen by several physicians, with no relief from her symptoms.

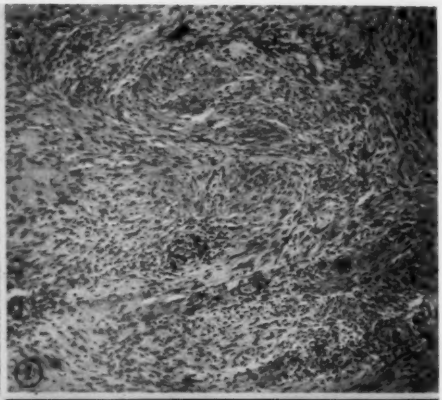
In May 1955 examination revealed a tender mass in the lower angle of the right popliteal fossa. A presumptive diagnosis of perineural fibroblastoma of the right tibial nerve was made.

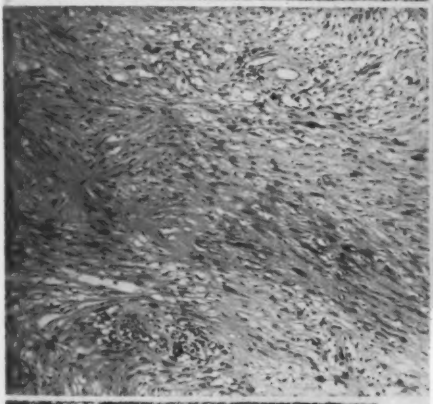
The popliteal area was explored under general anesthesia, and a 3 by 2 cm. tumor was found involving the tibial nerve. This was completely resected, and an end-to-end nerve suture performed with fine silk. The knee was placed in a plaster cast at an angle of 145° to prevent tension on the suture line. The postoperative course was uneventful. She was discharged with only slight pain on the fourth postoperative day.

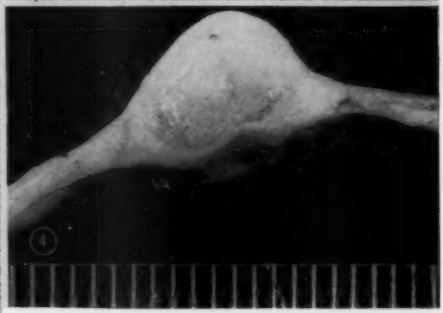
Pathologic report. The specimen consisted of an ovoid mass of tissue measuring approximately 35 mm. in length and 22 mm. in diameter. It consisted of fibers running lengthwise through the mass. On section, the central portion appeared to consist of a cyst 22 mm. in diameter, with a peripheral layer approximately 3 to 4 mm. in diameter, consisting of a gelatinous light-yellow material, and a central rounded zone 7 mm. in diameter which was firm, granular, and gray-tan in appearance.

Microscopic examination revealed a portion of peripheral nerve, within which there was an encapsulated tumor mass (figure 2). This contained a central area which was densely cellular, and a peripheral area which was sparsely cellular. In the former zone, the cells possessed indefinite cyto-









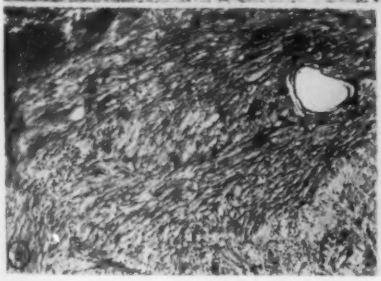


FIG. 1. *Case 1.* Photomicrograph, perineural fibroblastoma. Hematoxylin and eosin stain.
FIG. 2. *Case 2.* Perineural fibroblastoma. Hematoxylin and eosin stain.
FIG. 3. *Case 3.* Perineural fibroblastoma. Hematoxylin and eosin stain.
FIG. 4. *Case 4.* Gross specimen.
FIG. 5. *Case 4.* Perineural fibroblastoma. Hematoxylin and eosin stain.

plasmic outlines and elongated nuclei. These cells tended to be arranged in interwoven parallel rows. They were fairly uniform and orderly, though an occasional large bizarre cell was noted. There were no mitotic figures. The sparsely cellular areas contained small quantities of a fibrillar eosinophyllic material and numerous spaces which presumably had contained lipid. The cells were smaller but otherwise similar to those in the densely cellular area. There were numerous deposits of a densely granular pigment throughout and fairly many eosinophils. Diagnosis: Perineural fibroblastoma.

Case 3. A 70 year old, right-handed, white male diabetic was first admitted to the hospital on February 28, 1954, wtih a history of gradually increasing weakness of the right upper and lower extremities of one year's duration. It was noted that the patient had become forgetful and had difficulty with his speech and in naming obects. The patient was disoriented as to time and space, and it was noted that he had a steeple-shaped head with the protuberance in the left parietal area. Electroencephalography revealed a focus in the precentral and anterior temporal regions of the left hemisphere. A craniotomy was performed 11 days later, with removal of a large hyperostosis. Nine days later a second stage procedure was performed and a large left parasagittal meningioma was removed. This tumor had invaded the longi-

tudinal sinus and thrombosed it. The patient tolerated the procedure well and had an uneventful postoperative course. His right hemiparesis and aphasia improved. He was readmitted in March 1955 with a purulent discharge from the craniotomy wound. Removal of a tantalum plate was performed under local anesthesia. A large pyogenic membrane was also removed at this time. The postoperative course was characterized by an episode of diabetic acidosis. In April 1955 the patient began to complain bitterly of a severe constant pain in the right anterior thigh, radiating down the anterior aspect of the thigh and the medial aspect of the leg. This pain was not completely relieved by narcotics. Palpation revealed a tender, mobile, discrete mass in the medial aspect of the anterior thigh, with radiation of pain on palpation to the medial aspect of the right leg. The preoperative clinical diagnosis was perineural fibroblastoma.

Under field block anesthesia the mass was exposed and found to be a 7.5 by 3 cm. tumor involving the saphenous nerve. It was extremely adherent to the nerve trunk and the entire mass was resected with 1 cm. of nerve on either side. The patient's postoperative course was smooth, with disappearance of pain. The extremity, which was quite paretic preoperatively as a residual of his meningioma, showed no increased motor weakness. The patient was free of pain when last seen in November 1955.

Pathologic report. The specimen consisted of a 7.5 cm. long segment of peripheral nerve. Located in the center was a fusiform, smoothly outlined swelling which on cut section was seen to be composed of soft yellow tissue. Several small cysts containing thin red fluid were noted.

Microscopic examination showed the tumor (figure 3) to be composed of interlacing bands of spindle cells with elongated nuclei. There was a slight tendency to palisading. Much of the tumor was made up of round cells with clear cytoplasm and small round nuclei. In some areas whorls of collagen were prominent. The cysts did not have a differentiated lining. Most of the cells were quite regular, but a few multinucleated and bizarre forms were noted. Mitoses were very rare. Diagnosis: Perineural fibroblastoma.

Case 4. A 57 year old white man noted a swelling in his right knee and pain in the lateral aspect of the right foot early in 1953. Within a few weeks the swelling of the knee subsided. The pain in the foot persisted and increased in severity, so that he was forced to remain in bed for almost five months to avoid the extreme discomfort. Several months before coming to the hospital, the patient noted a painful nodule along the lateral aspect of the lower portion of the right leg when he stepped on his right heel.

Examination confirmed the presence of a firm, pea-sized tender nodule at the junction of the middle and lower thirds of the right leg along the course of the sural nerve. Sensation was slightly impaired in the area supplied by the sural nerve.

Operation was done with the use of local anesthesia. A firm, grayish-white nodule (figure 4) about 10 to 12 mm. in diameter was removed, along with a short segment of nerve proximal and distal to the tumor. The patient improved almost immediately. He continued to complain of slight pain for several more weeks, but finally he was almost completely symptom-free.

Pathologic report. The specimen consisted of a segment of nerve 5 cm. long and up to 0.5 cm. in diameter. At the center of the resected segment there was a grey, firm nodule about 0.8 cm. in diameter. On section, the tissue had a gray, somewhat gelatinous appearance.

Microscopic examination showed a mass completely encapsulated by a thickened perineurium (figure 5). Within this nerve sheath there was a proliferation in one area of elongated cells which were arranged in pseudo-palisades. Surrounding this zone there was considerable fibroblastic proliferation in a loose fibrillary stroma which resembled myxomatous tissue. Diagnosis: Perineural fibroblastoma.

DISCUSSION

It is impossible to consider all the causes of lower extremity pain without writing an exhaustive treatise. That solitary tumors of peripheral nerves are rarely mentioned as a cause of such pain seems odd, unless this disorder is so uncommon that most clinicians never encounter it. From a neurologic point of view most patients with unilateral lower extremity pain are studied as examples of nerve root or spinal cord disease. The criteria for establishing a diagnosis at the nerve root or spinal cord level are well known. Spinal puncture with investigation of the cerebrospinal fluid dynamics and chemistry and the use of opaqe contrast media myelography have become essential adjuncts in confirming the presence of intradural or extradural nerve root compression. Solitary tumors of peripheral nerves are often overlooked, mainly because they are not considered as a cause of pain and also because careful and complete palpation of the peripheral nerves is more or less neglected. In the four cases in our group, the tumor was discovered first by the patient in three instances. In case 3 pain was present for several weeks and many examinations were carried out before the tumor of the saphenous nerve was finally discovered and removed.

The pain in all four patients of this series was constant and intractable and not influenced by rest or activity. Though not as severe as the pain endured in causalgia, there were some elements which resembled this disorder. The pain occupied the center of consciousness during every waking moment, so

that the victim was soon completely demoralized and reduced to a pitiful subect constantly demanding medication for relief. The removal of the peripheral nerve tumor was followed by complete relief of pain or by marked improvement in our patients.

Among the more unusual causes of lower extremity pain, tumors of the high thoracic or cervical cord must be considered. Gross[6] reported an intraspinal epidermoid tumor at the fourth thoracic segment with symptoms of bilateral sciatica recurring over several years before the lesion was discovered. Scott[7] recently referred to high thoracic and cervical tumors as causing burning or sharp pain in the lower extremities. He indicated the need for performing complete myelography when lesions of the cauda equina or lumbosacral roots are not demonstrated by a more limited investigation.

Arterial disease may escape detection, and patients with aortic or common iliac obstruction who have lower extremity pain are often treated from an orthopedic standpoint for many months before the true nature of their disorder is discovered.

Primary or metastatic neoplasms of the pelvis or lower extremity may be overlooked as causes of lower extremity pain. Adequate x-ray examinations should obviate errors in these conditions. Many other causes of lower extremity pain could be listed. It is evident that a patient with obscure lower extremity pain requires a detailed systematic investigation, including careful palpation of the peripheral nerves, if the correct diagnosis is to be made.

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■ The view once held that the posterior columns of the spinal cord are made up of bundles of fibres passing from the posterior roots of the spinal nerves to the sensorium has proved to be untenable. Transverse division of these columns produces in the parts behind the section, *not* numbness, as it would do if these columns were simply the continuation of the posterior roots of the spinal nerves, but hyperaesthesia; and the pain resulting from the section is found to be due, not to any sensitiveness in the columns themselves, but to the irritation having extended to the posterior roots of the spinal nerves. Transverse division of these columns produces in the parts behind the section, not paralysis, but loss of co-ordinating power, such as is seen in locomotor ataxy.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

Metachromatic Form of Diffuse Cerebral Sclerosis

2. Diagnosis During Life by Isolation of Metachromatic Lipids from Urine

James H. Austin, M.D.

IN ORDER to diagnose a disease conclusively during life, specific tests are required. Laboratory tests also help to study the disease and to follow its progression. Diagnostic laboratory tests have not yet been available for those diseases still classified broadly, and imperfectly, as "demyelinating." This lack is becoming particularly important because of the growing need to identify the metabolic processes by which myelin is built up and broken down in health and disease. The unique disease discussed below has offered a model illness to study during life—one having both a diagnostic and research approach to each of these considerations.

Since 1953 five children in three different families with a progressive demyelinating disease of the central nervous system have been investigated. This particular disorder is genetically determined and is one of the several forms of diffuse cerebral sclerosis.[1,2,13] It has been termed either the metachromatic form of diffuse sclerosis or metachromatic leukoencephalopathy.[3–7] The term "leukoencephalopathy" is used because the brunt of the degeneration falls on myelinated axons of white matter. The word "metachromatic" describes a characteristic staining reaction of clumps of materials found chiefly in the areas of demyelination. Viewed microscopically, these granular clumps are shades of red when stained with blue basic aniline dyes. They stain a color other than that of the dye used, that is, metachromatically. A number of histochemical observations have suggested that these metachromatic clumps are lipid-carbohydrate in nature.[3,5,6] It is likely that their striking color change also reflects a high molecular weight structure, rich in freely dissociated acid groups, and thereby negatively charged.[8,9] The in vivo potentialities of large compounds somewhat analogous to "biological magnets" are understandably of profound functional interest. One reason for this interest is the parallel found with heparin and discussed further below.

Of more practical application in the present communication is the fact that, in this disease, metachromatic materials also occur in organs outside the nervous system. In particular, their deposition in kidney tubules has permitted the diagnosis to be made for the first time during life in five cases. The technic of microscopic diagnosis and the control studies supporting its specificity have been discussed in full in a previous communication.[9] In brief, this microscopic test and the following method depend on three principal observations: first, that the abnormal metachromatic granular material in kidney tubule cells does enter the urine; second, that it may there be separated out by centrifugation; and third, that the granular structures or their extracts still stain metachromatically under the microscope or when applied on filter paper.

After the initial microscopic stages in the study, two further needs were apparent. One was a practical method of diagnosis requiring a minimum of interpretation; the other was a means for a preliminary isolation of the small quantities of metachromatic lipids which would at the same time still preserve the other lipid fractions for study. Approaches and results of both are closely interrelated and form the subject of this communication.

To characterize the relatively small amounts of abnormal material available, 24-hour urines were processed. A technic was also necessary which would concentrate and purify abnormal metachromatic lipids out of that complex potpourri of substances to be encountered in urine in health or in disease states. These contaminants include other lipids, as well as non-lipid metachromatic susbtances such as acid mucopolysaccharides. Urinary granular material readily went into solution in a chloroform-methanol mixture. This observation suggested that this lipid solvent mixture could be successfully used as a first step in isolation.[9] Details of the approach which then followed are given not only to help the clinician understand the results, but also because the procedure has a wider applicability to the gen-

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This study was supported jointly by Grant S.G. 123 from the National Multiple Sclerosis Society and by Public Health Training Grant 2-B-5025.

eral study of lipids obtained in small quantity from complex biologic fluids or tissues. The procedure and its principles will be pertinent to later phases of this particular study as well.

As a further result of the separation procedures, a grossly visible diagnostic color spot test has been devised for this disease. It is simple enough for a routine clinical laboratory test. As in the previous study, a point has been made to test its specificity both against relevant abnormal as well as normal controls.

CLINICAL MATERIAL

Four patients with the metachromatic form of diffuse sclerosis were available for study during life (J.C., W.T., T.M., and C.M.).[9] Advanced signs of the classic clinical disease were present. Each was bedridden, with evidence of bilateral pyramidal tract signs, dementia, and optic atrophy. Duration of disease was four, four, six and six years, respectively. One patient (W.T.) has since died and the diagnosis has been confirmed by autopsy. Three separate families are represented. Diagnosis of the metachromatic form of diffuse sclerosis made during life by the tests described is proved pathologically by two autopsies in the *C* family, by two autopsies in the *T* family, and by renal biopsy in the *M* family. Unaffected parents and siblings whose urine sediment was negative provided one clinical control group; other pertinent disease states provided the abnormal control group essential to evaluate the specificity of the study.

DIAGNOSTIC PROCEDURE

In the first series of steps, sediment lipids are collected, separated, water washed, and dissolved in an efficient solvent, all under conditions of refrigeration. Twenty-four-hour urines are collected via finger cot or catheter through a sterile rubber tube into a clean shielded polyethylene bottle. A container of ice cubes surrounds the bottle to keep urine constantly chilled. Other preservative technics carry no special advantages under these circumstances. Volume and pH are recorded at the end of collection. All glassware is chemically cleaned. Urine is promptly spun at 4° C. in a series of 50 ml. cone-tipped centrifuge tubes at 1,500 r.p.m. for 20 minutes or longer until sediment is well packed. Supernatant is poured off, with care taken to lose no sediment. Sediments from several tubes are then combined in one final tube. Transfers are made by stirring with a glass rod and resuspending sediment in distilled water at 4° C. After centrifuging again, as above, sediment is twice suspended in cold distilled water, respun, and supernatant poured off. This final, doubly-washed sediment should be firmly packed so that a minimum of water remains layered above it. Twenty-five ml. of chloroform-methanol (2:1 by volume) at 4° C. is added to sediment, stirred thoroughly, and the suspension poured into a glass-stoppered reagent bottle. Sediment remaining in the tube is transferred with a second 25 ml. of chloroform-methanol. During this step, sediment lipids have passed into solution.

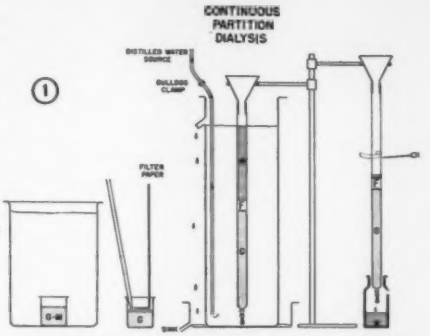

FIG. 1. Continuous partition dialysis. In center diagram cellophane bag is suspended in distilled water. Extract has formed three phases. W = water phase; F = fluff phase; C = chloroform phase. At right, aqueous phase is further separated by gravity. Needle indicates small marked holes made previously, out which water flowed. After freezing fluff, chloroform phase is similarly separated from below.
Diagram at left: Clinical laboratory test. Extracted lipids in small beaker are first washed in large jar of water. Beaker is removed and water suctioned out. White fluff is blotted up by folded strip of filter paper for staining with toluidine blue.

In the next stage the dissolved lipids are separated from undissolved sediment, water washed, partitioned during dialysis into three phases, and the phases finally separated. This process has the advantage of concentrating metachromatic lipids in the second phase; the other two phases are still saved for separate analysis. The important general principles and basic approach of this useful method are those originated by Folch and coworkers in 1951[10] and successfully applied to brain lipids. These have been modified by the Chatagnons[11] and Sperry[12] and further modified in details and improved in manner of separation to fit special needs and smaller lipid quantities of the present investigation.

One end of a wet cellophane tubing of ¾" diameter is knotted three times; the other is slipped snugly over the spout of a powder funnel and becomes firmly adherent as it dries. A ring stand holds the funnel rim and the pretested dialysis tube is suspended beneath (figure 1). Funnel serves both to support the tubing, to aid in filtering or washing, and as a reservoir to decompress osmotic pressure developed in the tubing. Several tubings may be readily processed simultaneously; 24-hour urine extracts may be pooled if necessary to increase the quantity. One folded piece of Schleicher and Schuell sharkskin filter paper is placed in the funnel (paper previously exhaustively extracted with boiling ethanol in a soxhlet to render it fat-free).[12] Tubing and stand are

transferred to the cold room at 4° C. for the following steps. Storage bottle is shaken to suspend its sediment, and its 50 ml. of lipids in solution enters the dialysis tubing through the filter. Insoluble sediment is retained on the filter. Ten ml. of solvent rinses out the bottle, then rinses off the filter, and enters the tubing. The tubing is then placed in a large covered cylinder of distilled water at 4° C. (figure 1). Fresh water enters cylinder from the bottom by gravity and leaves at the top by overflow. As this water dialyzes into the bag, the retained lipids are actively washed. Contaminating small molecular impurities dialize out and cholorform sinks to the bottom. As methanol rises, certain lipids originally soluble in the mixture are no longer soluble in either water-methanol or chloroform alone. These lipids slowly gather as the pure white "proteolipid"[10] phase referred to as "fluff" (F). This lies separated at the interface between the lower clear chloroform (C) and upper clear water (W) phases.

After a set period of 48 hours of dialysis against 22 liters of water, tubing is removed and suspended as before by funnel and ring stand. Tubing outside the chloroform phase is first allowed to dry and to shrink as much as possible. This lessens later shrinkage which raises the upper level of chloroform and fluff. The simplified separation which then follows takes advantage of gravity flow, of differences in solvent freezing points, and of the ease of penetration of cellophane. Most of the liquid water layer (W) is separated first. A row of small holes is carefully made 3 cm. above the fluff layer with a sharp No. 24 hypodermic needle. A tab of adhesive cellophane tape is applied just above to mark hole sites. Released water runs out, down the outside of tubing, and drips into a storage bottle. Both lateral jets of water and escape of water or fluff during later expansion are avoided by small holes, properly placed. Inside and lower outside of tubing are further washed off with 15 ml. of distilled water added slowly through the funnel. Care is taken both at this step and at all later steps not to disperse fluff into the aqueous phase. A small curved pipette introduced through a larger hole gently suctions most remaining water directly into the storage bottle. This technic avoids later water loss out holes from upward expansion during freezing. Stand and tubing are next taken to —30° C. Fluff (F) freezes in position against the inside of tubing, but chloroform phase (C) still stays liquid beneath it. At —1° C. the lower chloroform phase is then separated out from under the fluff by gravity. Chloroform flows down directly into another storage bottle through a second series of larger holes in the bottom of the tubing. Tubing is then taken to 4° C., cut off below frozen fluff phase, and inserted into a graduated centrifuge tube (with stopper). Frozen fluff melts at the edges and is quickly expressed (or cracked) into this open tube. Any adherent fluff is washed off tubing with 1 or 2 ml. of the aqueous phase into the same tube. Tube is centrifuged at 2,500 r.p.m. for one-half hour at 4° C. Supernatant water is suctioned off and rejoins original aqueous phase. After re-freezing, the small lower chloroform phase is poured into chloroform storage

TABLE 1

Category	*Patient*	*Age at Test (Years)*	*Diagnosis*	*Metachromatic Lipiduria Fluff Fraction*
PATIENT MATERIAL	J.C.	5	Metachromatic form diffuse sclerosis	+
	W.T.	9	Metachromatic form diffuse sclerosis	+
	T.M.	7	Metachromatic form diffuse sclerosis	+
	C.M.	8	Metachromatic form diffuse sclerosis	+
UNAFFECTED MEMBERS OF FAMILY	H.M.	40	Father of patients	0
	F.M.	32	Mother of patients	0
	B.M.	11	Brother of patients	0
	S.M.	14	Sister of patients	0
CENTRAL DEMYELINATING DISEASE	W.S.	16	Multiple sclerosis	0
	D.S.	5	Diffuse sclerosis	0
	S.E.	5	Diffuse sclerosis	0
	D.M.	35	Active acute multiple sclerosis	0
	M.L.	1	Encephalopathy of unknown etiology	0
HEREDO-DEGENERATIVE	W.H.	5	Progressive familial polioencephalopathy of unknown etiology	0
	J.A.	12	Gargoylism	0
	C.G.	11	Gargoylism	0
	D.M.	1	Niemann-Pick	0
RENAL DISEASE	B.B.	10	Pyelonephritis, hydronephrosis	0
	A.V.	70	Chronic glomerulonephritis	0
	J.A.	31	Hematuria	0
NORMAL AND ABNORMAL KIDNEYS	W.T.	9	Metachromatic form diffuse sclerosis	+
	A	1	Normal	0
	B	32	Normal	0
	C	28	Normal	0
	D	42	Normal	0
	E	12	Chronic glomerulonephritis	0
	C.V.	32	Sudanophilic form diffuse sclerosis (Schilder's)	0

bottle around the displaced frozen disk of fluff. Cold methanol is slowly added dropwise to fluff, with agitation until the emulsion clears. The three phases are stoppered and stored at —20° C. for further studies.

In the final stage (limited for purposes of the present report to gross color diagnosis), fluff phase is concentrated on paper and stained with toluidine blue at an acid pH. This low pH will allow only the most acidic groups to dissociate freely. It discourages red staining of all but the most strongly metachromatic substances. It thus greatly increases the specificity of the color test. During forced air evaporation, 0.05 ml. of solution of fluff in methanol is gradually applied to a small spot on Whatman No. 1 filter paper. Paper is next immersed in a solution of 0.01 per cent toluidine blue 0 (National Aniline) in 0.5 per cent acetic acid for 15 to 30 seconds, then rinsed free of excess dye in 2 per cent acetic acid at a pH of 2.7. An immediate red-pink is a positive result. This red-pink stands out sharply against the blue background when strongly metachromatic lipids are present. Temporary fading of the red is restored by redipping the strip in acetic acid.

RESULTS

Spot tests on all four available living patients with this disorder have repeatedly shown red-pink metachromatic lipids in fluff fractions (table 1). Four unaffected relatives have had none. This control group indicates that, under conditions of the procedure, metachromatic lipiduria is confined to affected members of a family. It also confirms previous negative microscopic results on 14 unaffected relatives.[9] Some control urines may also normally contain varying amounts of fluff. This clearly indicates that metachromatic staining fluff alone is significant.

None of the pertinent abnormal clinical controls had reddish-pink metachromatic lipids in fluff or other two fractions (table 1). This indicates that other forms of active demyelination and other relevant heredo-degenerative diseases studied do not have metachromatic lipiduria. It also confirms previous microscopic results now negative in 102 control cases.[9] It is of special note that two of the other forms of diffuse sclerosis are included among these negative controls.

Other urines were deliberately chosen because they were grossly contaminated either by large amounts of red cells, white cells, bacteria, epithelial cells, or casts. These also contained no metachromatic lipids. These abnormal controls establish that other pathologic changes in kidney, which might coincide with this disease,[14] or that theoretical complications of the urine collection procedure itself do not cause the observed changes.

Extracts of a portion of 10 per cent formalin-fixed kidney with metachromatic nephropathy from an autopsied case (W.T.) yielded reddish-pink metachromatic fluff (as did occipital lobe white matter—figures 2, 3, 4). Equal portions of formalin-fixed kidney from a normal child, from four adults, from an adult with Schilder's form of diffuse sclerosis, and from one with chronic glomerulonephritis were negative (table 1). These observations establish the essential staining identity of fluff extracted during life from urine, with that finally obtained from kidney of the same patient at post mortem. They also indicate that normal and pathologic control kidneys do not yield this material. They thus confirm the link between the presence of this renal lesion and the metachromatic form of diffuse sclerosis in the brain. It is again of particular note that kidney from a proved case of Schilder's (sudanophilic) form of diffuse sclerosis is negative in the face of severe diffuse myelin breakdown in the brain (figure 4).

Use of cellophane tubing permits all three phases to be saved and tested separately for metachromasia after appropriate concentration by lypholization or evaporation. Metachromatic lipids from urine sediment did not go into the chloroform phase. Gentle handling of fluff avoided occasional movement of small amounts of metachromatic fluff from sediment up into aqueous phase. Manipulations of salt concentration did not appear essential in actual practice in this regard.

OTHER TESTS

Thionine, methylene blue, and nile blue A in 0.01 per cent solution in 0.5 per cent acetic acid also stain the fluff red on paper; controls show no color. Sudan black B 0.05 per cent, bromphenol blue 0.01 per cent, and 0.5 per cent ninhydrin in ethanol stain the spots of both normal control and metachromatic fluff the expected black, blue, and faint purple, respectively. The periodic acid Schiff technic[15] stains both patient and control fluff spots red. The red color also occurs when spots are exposed to the Schiff aldehyde reagent without previous oxidation by periodic acid. The anthrone test for sugars run in test tubes on concentrated fluff was a positive green in patients and usually less green in controls.[18] Biuret test in tubes was a positive pink-purple in both groups. The diphenylamine test for sugars on concentrated fluff was a positive pink in patients and usually less so in controls.[19]

Protamine abolishes or inhibits metachromasia of the abnormal lipids to a striking degree. As little as 3 mg. per cent aqueous protamine sulfate blocked the red color when spotted strips were

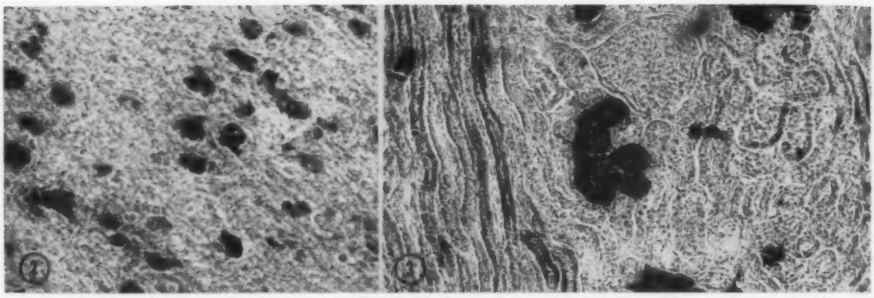

FIG. 2. Frontal subcortical white matter. Clumps of abnormal metachromatic materials seen here as black are not normally present. Case W.T. Frozen section. Toluidine blue 0.01 per cent aqueous, pH 2.7, was used for this and all subsequent figures.
FIG. 3. Convoluted and straight tubules of the kidney. Some tubule cells are filled with dark metachromatic materials. Case W.T. Frozen section. Toluidine blue.

dipped in it before staining. This concentration also obliterated the red color after previous staining. As expected, protamine was also found to block the red color of another metachromatic substance, heparin, when a spot of the latter was applied on filter paper. Paper electrophoresis was performed on Whatman No. 1 paper using Spinco apparatus model R and Duostat. Various current strengths were used over several different alkaline and acid pH ranges for runs over 16 hours. No metachromatic component migrated from the application point. (Specific conditions of interest included pH 8.6 barbital buffer, ionic strength 0.1, 240 volts, 30 hours; pH 10 borate-NaOH buffer, ionic strength 0.002, 250 volts, 44 hours.)

DISCUSSION

Test sensitivities. The whole 24-hour urinary output of metachromatic lipids is concentrated by this procedure into up to 0.2 ml. of fluff and 1 or 2 ml. of final methanol solution. In the four clinically advanced cases studied, only a small fraction of this solution of fluff (for example, 0.05 ml. or 1/20 of the total) might be used to demonstrate a visibly positive red-pink color when stained on filter paper. Only 0.01 ml. or less (that is, 1/100 of the 24-hour sample) has been positive in advanced cases. Considerably less total metachromatic lipiduria could be present, therefore, yet still be detected by increasing urine quantity.

The quantity of metachromatic urinary granular bodies has been observed microscopically to increase during the course of the disease. Similarly, the extracted metachromatic lipiduria increases in each patient as the disease progresses. It is also greater in the more clinically advanced of two siblings. A simple color quantitation may be made by grading an aliquot on a scale of one plus to four plus. Patients studied have been clinically in an advanced stage of the disease. The question was previously raised whether very early in the disease microscopic diagnosis could be made using a fresh sample of sediment from perhaps only two hours' output of urine.[9] The opportunity has not yet arisen to personally compare the sensitivity of the two methods in practice under these random conditions. It seems best, meanwhile, to regard the microscopic and fluff-staining spot tests as complementary. In the earliest possible case it may be necessary to do many separate microscopic examinations and combine several 24-hour sediments for spot test diagnosis. It should be noted that a different skill in visual interpretation is required in the former. Consequently, the two tests are not exactly comparable.

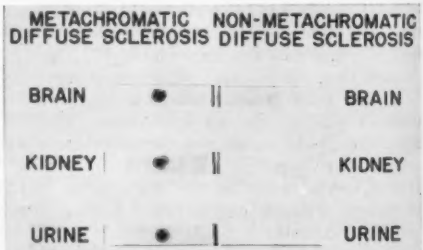

FIG. 4. Staining differences between lipids extracted from metachromatic and nonmetachromatic form of diffuse sclerosis. Equal portions of material are extracted from occipital white matter, kidney, and urine of contrasting cases. They are applied as a central spot on Whatman No. 1 paper strips. Toluidine blue. Film is not sensitive to red light. Red thus shows up as an undeveloped spot on the negative and as a black spot on final print. (Contrast Process Ortho, Eastman.)

This approach to diagnosis is based on the metachromatic nephropathy which accompanies overt childhood forms of metachromatic leukoencephalopathy. It is clear that the rare atypical case which has no renal tubular deposits will not be detected by this method.[16]

Color and staining considerations. On filter paper, abnormal fluff lipids rapidly stain red-pink with toluidine blue. For purposes of the present discussion, any immediate blue-purple hue instead of red-pink is not regarded as a positive test. Only later, as the paper dries, does the red-pink color of the abnormal fluff spot fade toward the blue-violet end of the spectrum. The immediate red-pink color does not fade grossly into the same golden-brown as does the granular material seen microscopically in kidney sections and urine sediment. Filter paper examined directly under the microscope shows no change in the red color to golden-brown. The complex polymeric nature of filter paper itself may influence these color reactions. The end point after fluff is applied to filter paper is much more definite than when any attempt is made to stain fluff directly in situ.

Observations on metachromasia and its blocking by protamine. Blocking of metachromasia of abnormal lipids in this disease by protamine is of more than casual interest. For purposes of convenience in discussion, it is helpful to think in terms of a model system. Here, metachromatic lipids may be considered to carry a negative charge because of their dissociated acid groups. Color blocking may then be interperted as the expected result when such highly acidic, negatively charged compounds are neutralized, as it were, in combining with highly basic, positively charged compounds like protamine. The observed blocking of the metachromasia of heparin by protamine, for example, might also be predictable from the known biologic antagonism of these two oppositely charged large molecules. Heparin is one of the most highly negatively-charged organic polyanions known. It seems reasonable that this outstanding physical-chemical property of heparin may be reflected in its many important biologic effects in vivo.[17]

What is the significance of the analogy between lipids in this disease and heparin? There are a number of reasons to consider that these metachromatic lipids may also behave as large acidic compounds not only in the laboratory, but in vivo as well. There, by analogy, their function may be viewed as possibly somewhat similar, in one sense, to a negatively-charged pole on a "biologic magnet." The important functional possibilities in health or disease of such highly negatively charged compounds can be appreciated, particularly when they occur in living systems as intimately dependent on discrete cation (+) and anion (−) electrolyte shifts as are brain and kidney.

It has been noted before that under the influence of formalin fixation some usually non-metachromatic substances (intracellular lipochromes, specifically) may take on the ability to stain metachromatically.[16] This point has previously been an important theoretical restriction on all histologic studies in this disorder, since they, of necessity, are done on pathologic material, usually formalin-fixed. In the present study it will be noted that metachromatic lipids were obtained under biologic circumstances from the urine during life. All further procedures on sediment were done under conditions of refrigeration without using formalin fixation. Metachromasia was also demonstrated at biopsy of one unfixed portion of kidney.[9,14] Metachromasia is thus considered to be a valid characteristic of this disease in vivo and not an artifact of fixation.

Nature of the metachromatic urinary lipids. Limitations in specific inferences which should be drawn from histochemical staining technics are well known and will not be further discussed at this time. In brief, the above stains, tests, response to protamine, and behavior in solvents are consistent, however, with a glycolipid structure, highly negatively charged, and existing in fluff with small amounts of protein components. It is of confirmatory interest that metachromasia should occur in the fluff phase because, when the brain is the organ extracted, fluff also contains most of one group of carbohydrate-containing lipids, referred to as cerebrosides,[10,11] as well as "proteolipids." The metachromatic moiety did not move away from other lipids remaining at the application point on paper in an electrical field at favorable alkaline pH. This may be one indication that these metachromatic components are bound as an integral part of the larger immobile lipid molecule. It indicates that free acid mucopolysaccharides contaminants, for example, are not responsible for the metachromasia. These would migrate under the circumstances.[20]

CLINICAL LABORATORY TESTS FOR METACHROMATIC LIPIDURIA

The procedure to be outlined follows principles previously noted and explained above. It requires no elaborate equipment and can be done at room temperature by the average clin-

ical neurologist without technical assistance (figure 1). Use of urines from normal and abnormal controls is suggested at first for contrast in color comparisons.

1. Twenty-four-hour urine specimens are collected on ice. One or preferably more complete specimens are centrifuged. This will depend on the clinical stage of the disease and the amount of metachromatic granular material present microscopically.

2. The centrifuged, carefully separated sediment is gradually transferred and collected into one centrifuge tube. There it is washed with water and respun until packed. Supernatant water is poured off. Any excess water overlying sediment may be removed by suction or filter paper wick.

3. Forty-five ml. of a mixture of chloroform and methanol (two parts to one part by volume) are added to the water-free sediment and stirred thoroughly with a glass rod. More solvent is added, if necessary, to sink and thoroughly extract all sediment.

4. The tube is again thoroughly centrifuged and the supernatant, now containing lipids in solution, is poured into a 100 ml. beaker or flask. This transfer may have to be made through coarse filter paper if all extracted sediment does not remain packed in the bottom of the tube.

5. A pipette is used to gently run tap water down the inside of the beaker. There the water is slowly layered over the surface of the chloroform-methanol until the beaker is brim full.[12]

6. The small beaker is slowly placed beneath the surface of a large jar (1,000 to 2,000 ml.) or jug previously filled with tap water. Washing continues overnight or until the white fluff phase lies completely separated above the chloroform. Beaker is then removed and only the water layer suctioned off. Care is taken not to disperse or lose the fluff. A wick of filter paper may be used to remove the last water at the edge of the meniscus.

7. Technic in this step will depend on the amount of fluff. Thickness of fluff is increased by using a washing container of smaller diameter. If fluff is sparse, it is all suctioned up in a pipette and delivered onto a spot 0.5 cm. in diameter on a strip of Whatman No. 1 filter paper. If more abundant, a filter paper strip bent at right angles near the end may be used. As much adherent fluff as possible is blotted up directly (figure 1).

8. After evaporation, the dry fluff area on paper is stained by dipping into 0.01 per cent aqueous toluidine blue in 0.5 per cent acetic acid. A red-pink color developing within one minute and persisting in 2 per cent acetic acid rinse is a positive result. Excess blue dye is gently rinsed off and red further developed in the acetic acid rinse.

SUMMARY AND CONCLUSIONS

1. A controlled study has been done on urine sediment from four living patients with the metachromatic form of diffuse cerebral sclerosis. Related procedures are described which provide both a simple diagnostic, clinical laboratory test for this disorder and a basis for more analytic studies.

2. Microscopic metachromatic granular structures previously reported in this disorder have been extracted from urine sediment. A further modification of the Folch washing procedure is used to partition and separate these sediment lipids into three phases. The fluff phase is spotted and stained on filter paper with dilute toluidine blue at an acid pH. A red-pink color results.

3. Only in affected patients are red metachromatic lipids concentrated in the fluff phase. Control sediments (and kidneys) from normal, from unaffected relatives, from the pertinent demyelinating diseases (including Schilder's form), heredodegenerative diseases, and renal diseases cited have not had metachromatic lipiduria.

4. Sensitivity of the spot test is such that the method described may be extended to diagnosis of earlier cases by increasing the quantity of urine studied.

5. The metachromasia observed is a property of these abnormal lipids as they are obtained under biologic circumstances from urine during life. It is thus a valid characteristic of the disease in vivo and not an artifact of fixation.

6. Solubility, staining, electrophoretic characteristics, and inhibition by protamine are consistent with a carbohydrate-lipid polyanion complex, having highly acidic, negatively charged components.

7. Metachromatic lipiduria parallels the clinical course of the disease. It increases as the disease progresses and is greater in the more advanced of two siblings.

8. In the same autopsied case, a microscopic correlation has been established between metachromatic granular material seen in brain and kidney and that seen in urine sediment during life (case W.T.). These microscopic observations are further supplemented by a correlation between metachromatic

lipids extracted directly from brain and kidney and those extracted during life from urine sediment of this same patient.

9. Metachromatic lipiduria and nephropathy are thus linked diagnostically with metachromatic leukoencephalopathy.

The author expresses his gratitude to the following persons for their valuable assistance in this study: Irving Hill, M.D. and Roy Dowling, M.D. for certain control urine specimens from patients under their care; Wallace Haug, M.D for tissues from a case of the sudanophilic form of diffuse sclerosis; and the nursing staff of the Doernbecher Memorial Hospital who participated in the collection of the specimens.

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■ Doctors Gall and Spurzheim do not admit of a common origin of the nervous system. They think that it must be divided and subdivided, and that each part of these divisions and subdivisions has its particular origin. They do not allow, therefore, that the spinal marrow and nerves originate in the brain and cerebellum. They are of opinion that the great sympathetic nerve has its source in various ganglia dispersed through the abdomen and thorax, independently of the brain. "The different parts of the brain, of the spinal marrow, the pretended cerebral nerves, and the nerves of the abdomen and thorax," Dr. Spurzheim says, "have their separate origin. The various parts are brought only into communication with each other." They consider the cineritious substance of the brain as the origin of the medullary, which they say is of a fibrous structure, and whenever any augmentation of medullary matter takes place, it is invariably traceable to a portion of cineritious substance. "In the foetus," says Dr. Spurzheim, "the whole brain consists of a cineritious mass, and it is only by degrees that the fibres appear."

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

An Electroencephalographic Syndrome Which Correlates with Severe Disruption of the Personality Structure

Ernst A. Rodin, M.D.

SINCE THE ADVENT of electroencephalography as a tool for diagnosis and research, a great many efforts have been made toward establishing direct relationships between function of the brain as revealed by electroencephalographic tracings and normal or abnormal behavior of the individual. The results of these studies in regard to normal behavior have been rather disappointing up to the present, although a great deal of data have been accumulated. Most of this work has been aptly summarized recently by Ellingson.[1] In regard to correlations between abnormal electroencephalograms and abnormal behavior, the group of illnesses termed convulsive disorders appeared to be the most important one by far. It was noted very early that, in most instances, a sudden change in the electrical events of the brain led to predictable behavioral alterations in the patient. These behavior changes might be a grand mal seizure, a petit mal attack, a complex psychomotor episode, or other focal seizures corresponding to the area of the brain which is temporarily deranged in its function. The group of patients who suffered from temporal lobe seizures proved most interesting for the study of abnormal behavior in relation to altered electrical activity of the brain because of the marked varieties of subjective and objective changes in the patient. Furthermore, it is fortuitous that most patients retain consciousness for a certain period of time and are able to describe their difficulties after the termination of the seizure or in some instances even during it. These subjective experiences were soon noted to be very similar to those experienced by "psychotic" or "psychoneurotic" patients. The main differences are that they are of much shorter duration in the seizure patient and that they tend to be repetitive, by which is meant that usually the same type of symptoms tend to recur in the seizures, although there are some very definite exceptions. It was found that a considerable proportion of patients with temporal lobe seizures also have, independent of their attacks, a large measure of psychiatric difficulties which prevent them from leading useful lives or allow for only a marginal social adjustment. As a general rule, it is possible for the electroencephalographer to state the likelihood of temporal lobe type seizure phenomena to be present clinically if a definite unilateral or bilateral focal abnormality in the temporal areas is found. This can be done from the appearance of the tracing alone without knowledge of the patient's signs or symptoms. However, it cannot be predicted confidently from the appearance of the focus alone whether the personality structure of the individual—independent of the seizures—is likely to be intact or severely disturbed. During the past year the author has gained the subjective impression that there exists a group of patients who have a marked diffuse slowing of the background rhythms, in addition to the focal discharge in one or both temporal areas. The combination of these two factors made it virtually certain in the cases observed that the particular patient had either a temporal lobe type of convulsive disorder and a severe disturbance in his personality structure or the latter alone. Therefore, it was of considerable interest to determine how accurate a prediction of this kind would be if nothing were known about the patient apart from his electroencephalogram.

MATERIAL AND METHODS

In order to put this subjective impression to analysis, it was decided to select from all electroencephalographic reports between November 1, 1955 and October 31, 1956 those in which the record was described as showing definite focal changes in one or both temporal areas and a background activity of at least 50 to 75 per cent of the total recording time slower than 8 c/s. The criteria for the focal discharge were either delta waves, spikes, sharp waves, sharp and complex discharges in the theta frequency range, or continuous 3.5 to 4 c/s theta discharges. The amplitude of all these discharges had to be at least 60 microvolts, with the exception of delta activ-

From the Neuropsychiatric and Mental Health Institute, University of Michigan, Ann Arbor, Michigan.
Junior Prize Essay read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 25, 1957.

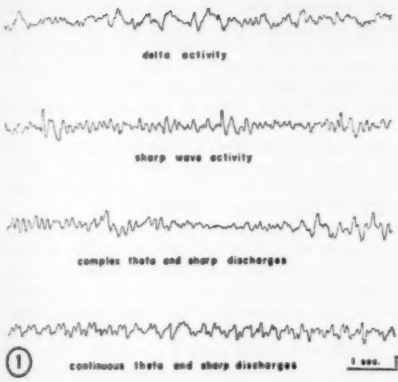


FIG. 1. Wave forms indicating definite disturbances in the temporal areas.

ity and continuous theta activity which was accepted with amplitudes ranging between 30 and 60 microvolts. Figure 1 shows the wave forms under consideration. Isolated theta discharges or high voltage hypersynchronous alpha bursts were excluded as not definite enough evidence for local pathology. It was not required that the focus be limited completely to the temporal areas; some spread into the frontomotor, parietal, or occipital area was accepted. The focus had to be maximal in the temporal areas, however, and cases showing independent focal abnormalities in other head regions were excluded. The focus had to be clearly present at least once every one minute of recording time. The criteria for background slowing were also strict. Scattered theta activity was not considered significant. The background frequencies had to be less than 8 c/s for prolonged periods of time covering at least five to ten seconds at a time. Recordings were discounted in which there was any question that the slowing of the background might have been attributable to drowsiness. Recordings of patients below age ten or above age 70 were excluded because of possible contamination of the sample with normal maturational and senile changes. Furthermore, it was thought that, if this electroencephalographic syndrome is detectable in records which were obtained during the aforementioned 1955-1956 period, it should be equally detectable from records of other patients which were obtained five years earlier with essentially similar recording technics. This would afford some control over the data gathered from 1955 to 1956, since none of the patients who were recorded from January 1 to December 31, 1951 were known to the author and the records had been interpreted by other electroencephalographers. For this reason all the electroencephalographic reports from the year 1951 were screened for this syndrome. The tracings of those cases which seemed to fit the stipulated criteria were then reviewed and all dubious cases were excluded. This screening method left 12 records for the year 1951 and 11 records for the year 1955-1956 which fulfilled all necessary qualifications. The clinical charts were then abstracted for age, sex, final diagnosis, chief complaint, brief history and symptoms, neurologic findings, psychiatric observations, psychologic test results, quality and quantity of medications which the patient was taking at the time of electroencephalographic recording, and whether or not the patient was incapacitated by his illness at that particular time. All records were obtained on a Grass 8-channel Model III electroencephalograph. A minimum of 12 and a maximum of 23 electrodes were used in monopolar and bipolar connections in the various records.

RESULTS

There was considerable agreement between the two groups of patients for various features, with some divergence for others. The clinical diagnoses are summarized for both groups of patients (table 1). A reasonably close agreement is seen, with the exception of three brain tumor cases in 1951; there was no proved brain tumor in the 1955-1956 series. Irrespective of diagnosis, the patients' chief complaints also show a fair agreement (table 2). A comparison of the duration of illness in the two groups of patients is shown in table 3 and some agreement can again be noted. Although only five patients in each group gave spells or epilepsy as the chief complaint, it was apparent from a review of the charts that 11 of the 1951 patient group had episodes suggesting temporal lobe seizures and the twelfth patient had questionable episodic disturbances. Of the 1955-1956 group nine patients had definite seizures and two had questionable spells. Seven patients of the 1951 group and five of the 1955-1956 group had major seizures in addition to the minor attacks. However, in both groups these were infrequent in occurrence and not the main problem. The outstanding symptoms were pronounced psychiatric disturbances and frequent minor spells which occurred more than once a day in most instances. There were some differences in the

psychiatric observations between the two groups. The disturbances in this sphere could be classified mainly as: disturbances of affect, thought, orientation, and memory, as well as hallucinations and paranoid ideation independent of seizures (table 4). Memory disturbances, disorientation, and confusion seemed to be somewhat more prevalent in the 1951 group, while there was apparently more evidence of depression, anxiety, excessive mood swings, disturbances in thought, and hallucinatory experiences in the 1955-1956 group. The terms infantile and immature were employed six times to describe the personality structure of the individuals in the latter group while they were used only once in 1951. If one examines the economic status of the patients of both groups, one finds very close agreement. Of all the eight males in the 1951 group, six were incapacitated by their illness to the extent that they could not hold a responsible job; one male patient was about to be dismissed from his work and another patient was in a penal institution. Of the four women, two were completely incapacitated and two were capable of performing some housework. The situation was similar in the 1955-1956 group. All five men were incapacitated; none was holding a job. Three women were incapacitated, while three others were able to do some housework. Some representative cases are described.

Case 1. A 17 year old girl was seen in 1951. There was no chief complaint mentioned. The history revealed that she had suffered a skull fracture two years before and had been comatose for two weeks at that time. On recovery she was noted to be aphasic, but this improved gradually. Three months after the accident she developed grand mal seizures and minor seizures. The neurologic examination at the time of admission showed anomia on rare occasions, a left lateral rectus palsy, a right central facial palsy, minimal nystagmus, and minimal decrease in the strength of the right extremities.

The parents stated that the girl is deteriorating; she is overly shy, does not date, is unable to sustain any interest for any kind of task, is easily discouraged, and performs completely unsatisfactorily in her schoolwork. The Wechsler-Bellevue test showed a verbal I. Q. of 90, a performance I. Q. of 82, and a full scale I. Q. of 85. The patient failed easy problems, but was able to solve those at an 18-year level. She was still somewhat dysphasic and had lowered immediate memory (on digit span) and lowered concentration (on arithmetics). The examiner also noted feelings of insecurity, impulsiveness, and rejection. At the time of the electroencephalogram the patient was on 100 mg. of Dilantin four times a day and 32 mg. of phenobarbital three times a day. The electroencephalogram showed the maximum of abnormality in the left temporal area, with some spread to the frontal region and some spread to homologous areas on the opposite side. The background frequencies varied between 5 to 6 c/s and 7 to 8 c/s (figure 2). The final diagnosis was convulsive disorder, posttraumatic; aphasia.

Case 2. A 53 year old woman was examined in 1956. Her chief complaints were abdominal pain and vomiting of four years' duration. She

TABLE 1
COMPARISON OF FINAL DIAGNOSES IN THE TWO GROUPS OF PATIENTS

	1951	*1955-56*	*Total*
Convulsive disorder	6	7	13
Brain tumor	3	0	3
Brain tumor suspect	0	1	1
Psychoneurosis	1	1	2
Schizophrenia	1	1	2
Aphasia, apraxia	1	0	1
Psychotic depression	0	1	1
Total	12	11	23

TABLE 2
COMPARISON OF CHIEF COMPLAINTS IN THE TWO GROUPS OF PATIENTS

	1951	*1955-56*	*Total*
Spells or epilepsy	5	5	10
Headaches	3	2	5
Inability to walk	1	0	1
Bad odor	1	0	1
Loss of memory	1	0	1
Abdominal pain	0	1	1
"Nerves"	0	1	1
No complaint	1	1	2
None mentioned on chart	1	2	3
Total	13	12	25

(One patient had headaches and spells in each group)

TABLE 3
DURATION OF THE ILLNESS IN THE TWO GROUPS OF PATIENTS

	1951	*1955-56*	*Total*
5 months to 2 years	3	1	4
2 years to 5 years	1	3	4
5 years to 10 years	2	0	2
10 years to 30 years	6	7	13
Total	12	11	23

TABLE 4
DISTURBANCES IN AFFECT AND THOUGHT PROCESSES IN THE TWO GROUPS OF PATIENTS

	1951	*1955-56*	*Total*
Affect flat	0	1	1
" inappropriate	3	3	6
" depressed	3	7	10
" euphoric	4	1	5
" anxious	1	5	6
Excessive mood swings	2	6	8
Illogical thinking and blocking	3	6	9
Paranoid ideation	2	3	5
Disorientation and confusion	6	2	8
Memory disturbed	5	1	6
Hallucinations independent of seizures	1	5	6

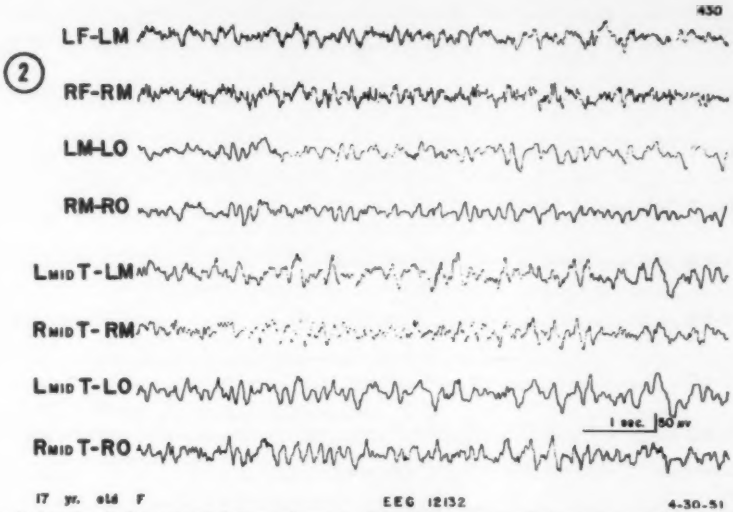


FIG. 2. Sample of electroencephalogram of case 1. Note the maximum of slow wave activity in the left temporal areas and the diffuse background slowing. The final diagnoses on this patient were posttraumatic convulsive disorder and aphasia.

had been in poor physical health most of her life. She had had a total of nine operations, five of them abdominal procedures. In addition to the chief complaints, she had severe headaches which were mainly right-sided, dizziness, diplopia, staggering and unsteady gait; she has fallen several times. Other complaints included palpitations, numbness and tingling, tremor, gustatory sensations, a feeling of a lump in the throat, dysphagia for solid food, and dysuria. The system review was positive for all questions asked. The neurologic examination was normal, the skull roentgenogram was negative, and the spinal fluid protein content was slightly elevated to 53 mg. per cent. On psychiatric observation it was noted that the patient was very dependent, infantile, and immature. She had appeared somewhat depressed, but also had a grandiose air about her. The nurse's notes stated that the patient was confused at times and told the nurses, "you are trying to kill me, everyone lies to me." She cried frequently without giving any reason for it. She was also noted to speak incoherently at times and moved unsteadily. On the day of discharge the nurse noted: "Patient has many paranoid ideas and apparently hallucinates." There were no psychologic tests performed. At the time of the electroencephalogram the patient was on one tablet of Bellabarmine twice a day, 1 gm. of magnesium trisilicate three times a day, and two aspirin tablets.

The electroencephalogram showed bitemporal sharp and complex theta discharges and a background activity of continuous 6 to 7 c/s (figure 3). The final diagnosis was personality disorder—severe, passive aggressive type; psychoneurosis—severe, chronic with conversion reaction.

Case 3. A 34 year old woman came to the outpatient department in 1956 with the chief complaint of "epilepsy for 30 years." At age four she was found thrashing in bed and the diagnosis of epilepsy was made at that time. Subsequently she had a variety of different attacks, including: 1) Mere staring for one-half to five minutes. 2) Weakness of the left leg, inability to talk, loss of consciousness; she did not fall, but either stood with flushed face, shook all over, walked around aimlessly, or ran somewhere. After a severe attack she was aphasic up to two hours. 3) Severe fright. 4) Sudden pain, like a sharp point going through the head. 5) A buzzing sensation going through left side of body. 6) Amnesic episodes covering several hours.

There was no history of definite grand mal seizures. The minor seizures varied in frequency from one to six daily in spite of anticonvulsant drugs.

The neurologic examination was essentially negative. The skull roentgenogram was normal. On psychiatric examination, the patient was relevant and coherent but gave evidence of excessive mood swings. She also admitted to auditory hallucinations which were of brief duration but not associated with any of her spells. These consisted of hearing the voice of her mother saying "daddy died" or the voice of her deceased father saying "daughter, you are next." Psychologic examination revealed a verbal I. Q. of 104, a performance I. Q. of 103, and a full scale I. Q. of 104 (Wechsler-Bellevue scale). There was little scatter in the verbal area with the exception that digit span was lowered. She performed well on tests for

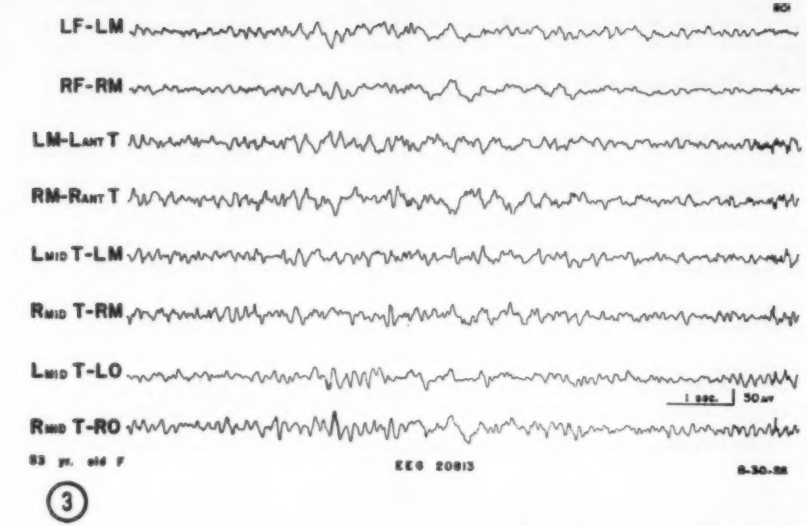
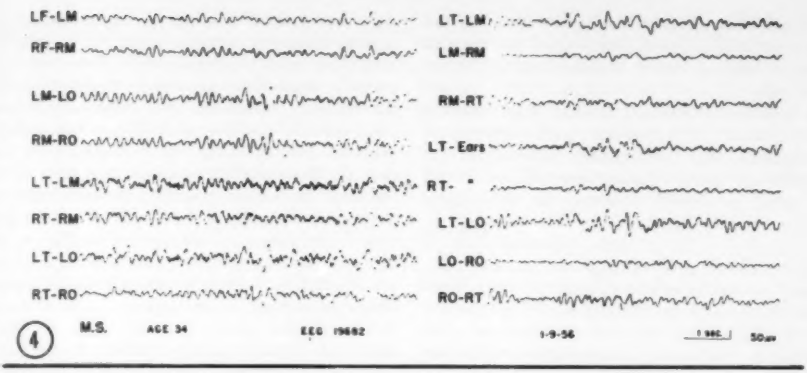


FIG. 3. Sample of electroencephalogram of case 2. Note the maximum of slow wave activity in the right temporal areas and the diffuse background slowing. The final diagnoses were severe personality disorder, passive aggressive type, and severe chronic psychoneurosis with conversion reaction.

comprehension, similarities, and arithmetics. In the performance area she did the block designs slowly but correctly. She was poor on digit symbols and inconsistent on picture arrangement, inasmuch as she arranged the easiest and most difficult series correctly. The Bender test gave no definite evidence for organicity; there were no distortions of designs. The Rorschach test revealed a great deal of fantasy living, some illogical thinking, and an autistic, immature, and impulsive personality structure.

At the time of the electroencephalogram the patient was on 100 mg. Dilantin three times a day and 500 mg. of Phenurone three times a day. The electroencephalogram gave evidence of sharp and complex theta discharges in the left temporal area and some isolated delta waves in the same region. The background rhythms varied between 5 and 7 c/s (figure 4). The final diagnosis on this patient was convulsive disorder, temporal lobe type.

Case 4. A 27 year old man came to the hospital in 1956 for a checkup on his convulsive disorder. He had had seizures since the age of five. These consisted of tonic spasms and clonic movements of the right arm, with decrease in consciousness and sometimes loss of bladder control. The head and eyes were turned to the right during the seizures. They usually lasted about five or ten minutes. Other spells consisted of simple faints without convulsion, or automatic behavior for several minutes with ammesia for the interval events. There were no seizures during the past year. Fourteen days before his admission to the hospital he became paranoid. He complained that people at his place of work were "egging him on" and "torturing" him. He thought that there were microphones planted in the house in order to get information about him. The neurologic examination was negative. The cerebrospinal fluid and a skull roentgenogram were also negative. On psychiatric examination he was noted to be oriented as to time and person, but was guarded and anxious in the interview. His affect was shallow. He had manneristic behavior and was also found to be inappropriate, circumstantial, and delusional. On psychologic testing the patient achieved a verbal I. Q. of 119, a performance I. Q. of 106, and a full scale I. Q. of 115 (Wechsler-Bellevue scale). However, the examiner felt that this did not represent the patient's usual state, as he was thought to have potentially superior intelligence. There was no appreciable evidence of an organic brain syndrome, and the patient had only mild difficulty with the block designs. The Bender test gave no evidence for organicity. The test behavior was regarded by the psychologist as clearly schizophrenic. At the time of the electroencephalogram the patient was on Dilantin 100 mg. four times a day, phenobarbital 32 mg. four times a day, and Mysoline 250 mg. four times a day. The electroencephalogram showed right temporal sharp and complex theta discharges. The background rhythms ranged in frequencies between 5 and 6 c/s, with some scattered low voltage fast activity (figure 5). The final diagnosis was convulsive disorder mixed type, psychomotor; schizophrenia, paranoid type.



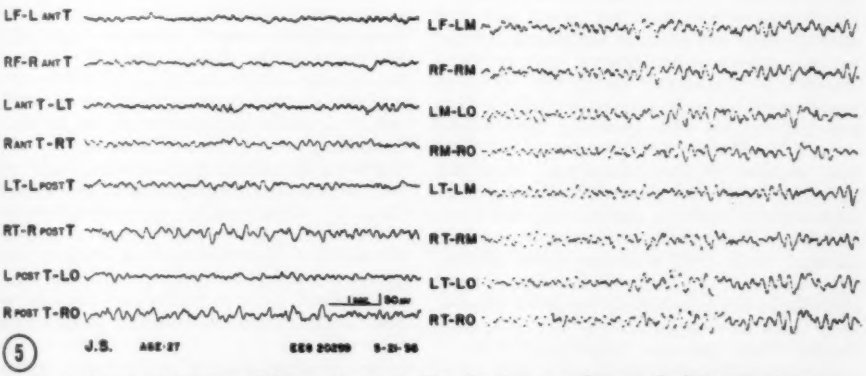


FIG. 4. Sample of electroencephalogram of case 3. Note the slow wave focus in the left temporal area and the diffuse background slowing. The final diagnosis was convulsive disorder, temporal lobe type.
FIG. 5. Sample of electroencephalogram of case 4. Note slow wave focus in the right temporal area and the diffuse background slowing. The final diagnoses were convulsive disorder mixed type, psychomotor, and schizophrenia, paranoid type.

DISCUSSION

It seems apparent from these data that the electroencephalogram alone does allow the prediction of a severe disruption of the personality structure in a selected number of cases. It is of interest that the three patients of the 1951 group and the four patients of the 1955-1956 group who had the most pronounced slowing of the background rhythms (continuous 5 to 7 c/s activity) were all regarded by at least one observer as definitely psychotic, with exception of one female patient who was apparently making a marginal adjustment. It is even more interesting when one considers that the psychoses of these patients did not present primarily an "organic" picture either clinically or on psychologic tests, but rather a picture which resembled the "functional" psychoses essentially of the schizophrenic variety.

Mundy-Castle and co-workers[2] presented material on 104 patients with senile psychoses and stated that 54 per cent of the psychotic group had abnormal electroencephalograms, mainly diffuse theta activity or theta and delta activities. These authors also pointed out that the increase of severity of the dementia tended to lessen the likelihood of presence of a normal electroencephalogram. Weiner and Schuster,[3] who investigated the electroencephalograms of 71 patients with dementia of various etiologies, also found a statistically significant correlation between clinical evidence of the severity of dementia and electroencephalographic slowing. The study reported here would suggest that it is not necessarily the dementia itself (meaning mainly the loss of intellectual capacities) which correlates with the electroencephalogram, since most of the I. Q. tests which were

performed on our patients were within normal range and the clinical features of an organic brain syndrome were outstanding in seven cases only.

A report by Stoller[4] showed that "mental deterioration" corresponded with slowing of the alpha rhythm. This author selected 20 out of 2,500 electroencephalograms which showed the most profound slowing of the alpha rhythm. Mental deterioration was found in at least 18 of the 20 patients. Thirteen showed mainly dullness and withdrawal, but five also showed excessive emotional instability. Epileptic seizures were present in 16 of the 20 patients, but in all patients the seizures were infrequent. It was not mentioned whether these episodes were grand mal convulsions or minor seizures. It was stated that all epileptic cases were of long standing except one and that age and sex were no significant factors, but the patients with epilepsy were predominantly in the younger age group. There is considerable agreement between Stoller's data and those which were presented here, which suggests that similar patients were observed in both studies. Stoller's recordings were obtained however on a 3 channel electroencephalograph machine and he may not have had the opportunity to see the focal temporal changes which could well have been present.

It should be pointed out that the present study lacks completeness as far as the psychiatric and psychologic evaluations are concerned. Only the most outstanding features were recorded and some patients may have had more psychiatric symptoms. The charts were written by a variety of clinicians at various levels of their training program and the information is spotty in parts. This might explain partially the differences between psychiatric observations in 1951 and 1955-1956. This difference might be more apparent than real, especially in the group of patients who had long standing convulsive disorders with predominantly minor seizures. While the absence of more extensive data is indeed a handicap, it tends to make the available information more significant. It is less likely that the material reflects a bias toward a certain type of psychiatric symptomatology which might be unconsciously introduced if all patients were seen by the same observer.

The problem of correlating electroencephalographic findings with psychiatric disease entities has been a rather thorny one in the past. Most authors agree that a larger proportion of patients with mental or emotional disorders show abnormal electroencephalograms than one would expect from sampling a normal control population.[5] However, it is equally true that abnormal tracings in the psychiatric population are frequently of the "non-specific" variety and that a fair proportion of severely disturbed patients have normal electroencephalograms at the time of recording. It would, however, be somewhat unreasonable to assume that a given symptom or set of symptoms should always be due to the same cause and, therefore, show a high degree of correlation with the electroencephalogram either in a positive or negative sense. If one thinks of the symptoms in terms of which neuronal circuits are most likely to be interfered with, irrespective of cause, one might gain a more fruitful viewpoint. The recent accumulation of data about the function of the "temporo-limbic system" makes it conceivable that in the not too distant future clinical syndromes will emerge dealing with specific disturbances in the psychic sphere, which might well be as easily recognizable as, for instance, Wallenberg's syndrome or the Brown-Séquard syndrome. A recent report by Ervin and co-workers[6] could be regarded as a step in this direction. These authors examined the behavior of 42 patients with "temporal spikes" and found a high incidence of episodic disturbances of a visceral, perceptual, affective, or ideational nature. Eighty-two per cent of these patients had the clinical diagnosis of schizophrenia. It is unfortunate that no description or illustration of the temporal "spike" and no description of the background activity were given. These are factors which are likely to be of importance. Description of the spike especially seems important in the light of a study by Pond and co-workers[7] and our own experience. Pond stated that patients who have spike foci in the temporal lobes are likely to have definite epileptic seizures, while patients in whom the focus is somewhat less classic present atypical and often bizarre attacks which have previously been called "hystero-epilepsy." Our own findings are in complete agreement with Pond's observation; it was somewhat surprising that all of the focal discharges observed were markedly slower than true "spikes." This could mean either that they arise at deeper structures or that the irritative process is not strong enough to produce classical seizure discharges.

The etiology of the described electroencephalographic syndrome is apparently diverse and cannot be determined from the tracing

alone. Frequently the syndrome is associated with long standing convulsive disorders of the temporal lobe variety. Since these patients are usually on moderate to heavy doses of anticonvulsant medication, this factor also has to be taken into account for aiding the development of background slowing. Future investigations will have to show whether or not the background slowing disappears when medications are reduced, even if this increases the danger of provoking major seizures. It is apparent, however, that medications alone cannot be responsible for the appearance of the syndrome in all patients, since six patients received no medication at all, two patients received Thorazine and reserpine alone, and two patients received medications which have no possible effect on the electroencephalogram. It is likewise not possible to attribute the appearance of the syndrome to seizures, since there were only 12 patients in the entire series who had major seizures at one time or another. It seems more likely that some form of cerebral irritative or degenerative process is taking place, which is as yet still poorly understood and which gives rise both to the seizure manifestations and to the interictal psychiatric difficulties. In three cases this irritation or degeneration was due to the development of a brain tumor, and it is of interest that these records were not markedly different from the rest of the group.

It seems justified to conclude that, if the electroencephalographer finds the described syndrome in an electroencephalogram, he may suggest to the clinician that this patient is likely to experience a rather severe disturbance in his personality structure. The patient may claim seizure control and it may not be apparent on a short visit that this statement is incorrect, either because the patient has a memory defect or because the seizures may have been replaced by severe depression with suicidal preoccupations. An electroencephalographic report of the type mentioned would then serve as a warning signal that the patient's psychic functions should be investigated closer. Finally, it would seem unlikely that the patient's symptoms in these instances are the expression of a mainly psychogenic process, which is implied when the diagnosis of conversion hysteria psychoneurosis or functional psychosis is made in these patients, and the diagnostic and therapeutic procedures should be directed toward abolishing or ameliorating the cerebral dysfunction.

SUMMARY

1. A limited series of cases is reported, in which an electroencephalographic syndrome is described which shows a high correlation with the presence of a severe disruption in the individual's personality structure.

2. The syndrome consists of the presence of marked focal abnormalities in one or both temporal areas and a background activity which is at least 50 to 75 per cent of the entire recording time slower than 8 c/s.

3. The electroencephalographic tracings of all patients recorded at the University Hospital during the year 1951 and during the year November 1955–November 1956 were surveyed. Twenty-three cases between the ages of ten and 70 years were found who met the criteria. A survey of the clinical charts of these patients revealed that all were profoundly handicapped in their psychic functions.

4. It is suggested that the electroencephalographer might direct the clinician's attention to this syndrome and its correlations if it is observed during an electroencephalographic examination. This may be of special practical importance in long standing cases of temporal lobe type of convulsive disorders who are regarded as controlled on their anticonvulsant program and in cases where a primarily psychiatric diagnosis is entertained on the basis of the clinical picture.

5. Since patients below age ten and above 70 were excluded from this study, no statement can be made regarding possible clinical correlations of the syndrome in these age groups.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Charles D. Aring, M.D. and Joseph Smith, M.D.*

A 21 year old man was admitted to the hospital on January 8, 1957. According to his father, his illness had begun at the age of 17 months when he had fever for five days, during which he had his first seizure. The convulsion was followed by left hemiparesis which had been permanent. There occurred a second seizure around the age of two years; thereafter he had no convulsions until the age of seven years. Beginning at the age of seven, he had had a series of two to five seizures weekly which were described as follows. A noisy vocalization was heard; he would then choke and become unconscious. The convulsive manifestations began in the left limbs and rather rapidly became generalized. During the attack he would usually be incontinent of urine and he had occasionally bitten his tongue. A seizure was followed by a period of confusion for minutes; he would remain listless for the remainder of the day. In the time between seizures he received 0.1 gm. of Dilantin three times a day; there had been some supplementation with phenobarbital in small doses for a period of a few months before January 1957.

The patient was examined on September 2, 1953 and the following abnormal signs were noted. The patient was poorly developed and poorly nourished. He had the scars of burns on his right forearm and shoulder sustained during a seizure. His intelligence was estimated to be considerably below normal. The optic fundi were normal. A left hemianopia was suspected on confrontation testing. The movements of the eyes were adequate in all directions and there was no nystagmus. His pupils were 7 mm. in diameter; they reacted slowly and through a poor range to flashlight. Sensation of the face was normal and the corneal reflexes were equal and active. Left lower facial weakness was obvious. Hearing was normal. Speech was thick. The uvula elevated in the midline and the tongue was protruded normally.

There was marked atrophy of the extremities and torso on the left. Tonus in the left limbs was increased somewhat; however, the fingers of the left hand could be hyperextended passively. It was estimated that strength throughout the lower extremity was of the order of about 50 per cent, and in the left upper extremity it was estimated to be about 10 per cent. His gait was of the typical hemiplegic type. All tests of coordination were performed very poorly with the left limbs. The sensory examination was almost impossible to evaluate, but the impression was obtained that perhaps he had some cortical sensory loss in the left limbs.

An electroencephalogram was generally very dysrhythmic, compatible with epilepsy between seizures. There was an irritative type of focus present in the right temporoparietal region.

In early 1956 he had become aggressive and combative for a day or two prior to seizures. In late December 1956 the patient's seizures became practically continuous throughout the day and night. At the time of his entry to the hospital (January 8, 1957), he was having seizures at the rate of one every five to ten minutes. These continuous seizures were described in such a manner as to suggest generalized tonic followed by clonic movements.

The patient was the third of seven children. He was born normally and the entire pregnancy was said to have been uneventful, terminating at full term. His developmental history was also normal; he had sat, walked, and talked at the proper times and his health had been excellent up until the advent of the feverish illness and seizures at the age of 17 months. He had never gone to school because of seizures; his mother estimated his intelligence to be below normal. The family said that the patient had rather frequent nosebleeds and right frontal headaches. Nothing else of significance was derived in the history, including the family history.

He was in coma when admitted to the hospital on January 8, 1957. There occurred repeated seizures in which it was sometimes possible to recognize a sequence of involuntary behavior as follows: a grunt, then the head turned to the left and the muscles of the left face twitched. His head then turned to the right; there was flexion of the left upper extremity and extension of the right limbs, though the right hand would flex strongly on the forearm. After this march, there occurred generalized tonic spasm, and in addition one could recognize slight clonic movement. An episode lasted from one to two minutes and then relaxation would occur. The pupils dilated during an attack, and there was foaming at the mouth with chewing movements. At the time of admission to the hospital no deep or skin reflexes could be obtained; there were bilateral extensor plantar responses and a left Hoffmann sign.

Temperature was 100.2° F. (rectally); pulse rate ranged between 88 and 100; blood pressure was 138/80. He responded infrequently to painful stimuli and would then jabber in a slurred manner. There was striking atrophy of the left extremities and torso; the left extremities were smaller in bulk and length. Between seizures the

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right pupil was 5 mm. and the left 3 mm.; they reacted slowly to light and through only a fair range. His mouth contained foul-smelling sordes and old and new bleeding from an abraded tongue. There was gum hypertrophy. Between January 9 and 11, when he was having less seizure activity, he was noted to have a spastic left hemiparesis, with adduction at the shoulder and moderate flexion of all the joints of the upper extremity. He could move the left lower extremity but there was little or no voluntary movement of the left upper extremity. Tonus was increased in the left limbs. His expression was staring and stupid; his mouth was held partially open. He obeyed some requests. There was slight ptosis on the left; the lower portion of the left side of the face moved less well than the right side. Although consciousness was obviously defective, it could be determined that he responded to pinprick throughout. No reflexes could be elicited in the left extremities. An extensor plantar response was constantly obtained on the left.

He gradually improved, although he slept a good deal in mid-January. He had epistaxis of bright red blood on January 13. He was able to be up in a wheelchair on that day. He had days when he seemed alert and cooperative. He would then want to get up in a wheelchair and talked about simple topics such as going out to play with the other children, but on a subsequent day he would not seem able to even swallow. Then he remained lethargic, slept for long intervals, and was incontinent of urine and stool. Sometimes he could not be aroused even to eat. During the period in mid-January, he had only a few seizures which began with extension of the left upper extremity. On several occasions he walked with assistance in a hemiplegic manner. He was never considered to be a suitable candidate for formal psychologic testing. In late January he was having up to a half a dozen short grand mal attacks a day without any obvious postconvulsive difficulty.

On January 8 and 9 Dilantin, 0.3 gm., was administered by rectum every three hours. During the same days he received 0.06 gm. sodium Luminal intramuscularly every four hours and fluids were administered intravenously. After January 9 he received 0.1 gm. Dilantin by mouth three times a day. On January 14 the Dilantin was discontinued and he was given Mebaral and Mesantoin, 0.1 gm. of each three times a day. This was continued until January 18, when he received phenobarbital 0.03 gm. and Mesantoin 0.1 gm. every eight hours. Before his operation on January 30, he occasionally received an intramuscular dose of sodium Luminal as a supplemental anticonvulsant.

The routine laboratory studies were normal, as was an analysis of the cerebrospinal fluid performed on January 9, 1957. His fever ranged around 102° F. (rectally) for the first three days of his hospital stay until the seizures were brought under some control. Electroencephalographic studies on January 15 and January 29 were similar, in that the records showed mainly a four to five per second pattern in all leads. The most significant feature was an atypical spike-wave pattern in all leads, which gave evidence of arising in the right temporal leads. There was no response to hyperventilation.

Roentgen study of the chest was normal; skull films showed that the pineal gland was not calcified. The cranial cavity on the right was considerably smaller than on the left, and there was increased thickness of the calvarium on the right. The frontal sinus and mastoid cells were larger on the right.

An air encephalogram done on January 22, 1957 revealed great dilatation of the entire right lateral ventricle; the left lateral ventricle was about normal. The third ventricle and the septum pellucidum were shifted toward the right. The fourth ventricle was not seen. There was a good deal of air in subdural spaces.

The patient was operated on January 30, 1957.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES D. ARING: I won't repeat what you can find stated in the protocol; I presume that most of you have read it. During my discussion I want to depart somewhat from the case described in the protocol to point up some general problems raised by it.

The main features of the case to which I want to draw attention are: 1) What happened to this patient at the age of 17 months? 2) Why was he so badly crippled and why did his disease progress to intractable seizures? and 3) Why did he come to operation? From all the information that has been reported, the patient was quite healthy up until the age of 17 months. I was among those who saw this young man when he was first brought to the neurologic clinic. At that time he was having intractable seizures and couldn't give a story; in fact he couldn't or wouldn't talk. But his father, who accompanied him, assured us that he had been perfectly well up until the age of 17 months and that he had developed quite normally to then. So something happened to change an infant developing normally into a badly lamed child. It is known that what happened to this boy occurs with fair frequency. In his excellent book on childhood neurology, Ford[1] noted that 200 cases of acute infantile hemiplegia had been seen at the Harriet Lane Home at the Johns Hopkins Hospital.

In children who suffer acute infantile hemiplegia of obscure origin, health has usually been excellent up until the time that the neurologic symptoms suddenly develop without warning. The symptoms usually may be ex-

plained clinically on a single gross vascular lesion. The child may have a seizure which may be jacksonian or grand mal. Almost always there is loss of consciousness, frequently vomiting, and usually fever of moderate degree. The seizures usually recur for hours or days and the child remains stuporous or comatose. Then the convulsive activity ceases and the temperature falls; the child slowly regains consciousness, when unilateral neurologic signs become obvious. The cerebrospinal fluid is usually found to be normal. Air studies done during the acute stage usually reveal swelling of the affected hemisphere. If air studies are done during a later stage, unilateral hemispheral atrophy is demonstrated. Deformities and spasticity develop in the involved limbs. These limbs do not develop as their mates, and tremor and other involuntary movements may appear in them. In about half the cases, seizures—either frequent or infrequent—have been recorded. As a rule these seizures are confined to the paretic side and, if not confined there, they usually begin there. There is some degree of mental defect. If the disorder is severe, frequent seizures develop as the patient becomes older. Early in the course in some cases the palsy remits, to reappear transiently after the seizures. In these acute infantile hemiplegias of obscure origin, there is never a recurrence of the paralysis after it has remitted. But a severe hemiplegia rarely disappears. Few of these patients die in the acute stage. The child usually recovers enough strength to walk, but the upper extremity usually is rather useless. As already mentioned, in one-half the cases epilepsy follows and mental deficits occur.

Established cases of infantile hemiplegia may be classed into three types. In one group the hemisphere is affected by vascular abnormalities associated with calcification of the cortex. This calcification appears particularly in the posterior portions and in occipital and parietal areas. Evidently our patient does not fit into this type, sometimes termed the Sturge-Weber syndrome. There were no calcifications in the roentgen studies of the skull.

The second grouping of these cases is that in which the territory of the brain supplied by the middle cerebral artery atrophies. As a result, a part of the brain is replaced by a cyst, usually communicating with the ventricle. This type of lesion is thought to be due to an occlusion of an artery, usually at birth.

The third grouping are the diffuse types of infantile hemiplegia where, after a period of normal development over one or two or more years, a sudden episode characterized by repeated focal seizures ushers in a complete hemiplegia, in which only partial or minimal recovery may take place. Our patient belongs in this latter group. In this diffuse group the evidence suggests that the lesions are maximal in one hemisphere. In some cases the opposite side of the brain may also be involved, but to a much lesser degree.

It seems reasonably clear that this patient suffered the onset of an acute infantile hemiplegia of the diffuse variety in which the whole hemisphere was involved. It is possible that the opposite hemisphere may have been implicated, too. We can't say from the clinical record. The electroencephalographic studies suggest that this was the case, and when he was in an obtunded state, having repeated seizures, such bilaterally innervated functions as swallowing and speaking were affected and bilateral extensor plantar signs were recorded. However, we know these signs with the spread of cerebral dysrhythmia as in status epilepticus when the entire brain function may become disorganized without there necessarily being lesions in both sides of it.

In differential diagnosis I suppose that we would have to consider the cerebrovascular lesions which follow on acute infectious disease, although we have no clear evidence of infection in this patient. It is said to be well known that lesions in the walls of cerebral as well as systemic vessels may be found in young subjects in almost all severe infectious disease processes. There are many cases in the literature reporting studies of infants who have had cerebrovascular lesions after infectious diseases. Destruction may occur in the media of large and small arteries particularly, and necrosis of the brain results.

Another condition that might deserve some consideration is thrombosis of one or more of the dural sinuses. As you know, this process in infants is usually a marantic affair if no sepsis is present. In the acute stage usually there is increased intracranial pressure, edema of the scalp and the eye, and distention of scalp veins. This condition usually is seen in infants between the eighth and ninth months in poor physical condition. These marantic occlusions of venous channels are usually associated with nutritional disturbances, anemia, diarrhea, and so on. If the superior longitudinal sinus is involved, hemiplegia is not uncommon. I am not inclined toward this diagnosis in this patient, since he was said

to be quite healthy at the time of the inception of his disease. Besides, death almost invariably results in these marantic infants who develop thrombosis of venous sinuses.

My reasoning is that this patient had an acute infantile hemiplegia of a diffuse nature and of unknown origin. The corroborative evidence lent by roentgen study of the skull and by the air study, particularly, supports this diagnosis as the reason for his poor mental and neurologic function. Why he progressively developed more and more seizures and increasingly ineffective brain functioning, I can't say. I suspect that the parents became discouraged with drug therapy, but we also know that some of these cases of infantile hemiplegias do have an accentuation of the number and severity of the attacks as they grow older. This point adds to the evidence.

The final part of my discussion I have reserved for some note about the operation on January 30, 1957. As far as I know, Krynauw[2] was the first to draw attention to the treatment of patients such as this by removing one cerebral hemisphere. In 1950 he reported on 20 cases. Since that time, there have been other reports concerning hemispherectomy as a treatment for the condition. The main reason for performing this extensive operation is particularly uncontrollable seizures, although cases have been so treated who have been unable to function very well mentally and physically, who have not had as much seizure activity as our patient. So this type of case, with a hemisphere that is severely and generally damaged, although not so badly that it ceases function altogether, a hemisphere that malfunctions so badly that it makes the whole organism ineffective and makes the patient a considerable burden to his family, is coming to hemispherectomy in increasing numbers.

Since I partook in some of the decision that led to the operation of this patient, I know why this man was brought to surgery. He was having intractable seizures and, although we did secure a modicum of control of his attacks, they left him functioning very poorly indeed neurologically. He was completely unable to care for himself. As Krynauw and others have shown, if the offending cerebral hemisphere is removed, which seems to discharge widely into the other parts of the brain that are more normal, then it is possible for many of these people to be returned to their families, to take care of themselves, and indeed in some instances to gain in intellect. In a surprisingly high percentage of cases the seizures have been completely relieved; in Krynauw's cases 83 per cent were free of seizures postoperatively without the patient needing to take medication. It has been an interesting observation that some of these patients have partial seizures after surgery, that is, they have the beginnings of a seizure which is certainly not as incapacitating as the continuous epilepsy that they had suffered prior to operation. Finally, it should be noted how little disability is added by the operation if the hemiparesis was sustained in early infancy. If hemiplegia came on later in life, the operation is apt to increase the disability.

DR. RICHARD W. VILTER: May we have the deliberation of the morning conference?

DR. DAVID BLANKENHORN: Nineteen students attended. The diagnosis of 17 was infantile cerebral hemiplegia. Two students felt that the original illness represented a bout of encephalitis and that the convulsions were residual effects of right hemiatrophy of the brain, with secondary atrophy of extremities and trunk.

DR. VILTER: May we see the roentgen studies?

DR. BENJAMIN FELSON: The difference in the two sides of the calvarium probably cannot be seen too well from the seats. I think you can see that the left petrous apex and mastoid cells are at a lower level than those on the right and that the air sinuses are very much larger on the right side. The calvarium is about 1½ cm. thick on the right and about ½ cm. on the left.

In the air study lateral views, we see a large air pocket which proves to be a part of the ventricle itself, there is tremendous dilation of the entire right lateral ventricle, including the temporal horn. In a frontal view this same lateral ventricle is tremendously dilated as compared to that on the opposite side. It is readily seen that the septum pellucidum is displaced toward the right, and the third ventricle even more so to the right. This indicates a much smaller hemisphere on the right than on the left.

The roentgen diagnosis is a marked cerebral atrophy involving the entire right hemisphere, which must date back to early life because of the smaller size of the right calvarium induced by bony thickening and secondary changes of elevation of the right mastoid cells and enlargement of the right frontal sinus.

DR. VILTER: Dr. Trufant, I believe you saw this patient on several occasions and followed him to surgery where you performed some

interesting observations during the operation.

DR. SAMUEL A. TRUFANT: Dr. McLaurin will tell you about the operation. After the skull flap was turned, we performed direct cortical recording. The electroencephalogram done in January of this year showed a diffuse dysrhythmia throughout, but in the right temporal lead there was a rather singular-appearing spike that was not seen elsewhere. We felt that this temporal spike was worth pursuing by recording from the cortex. In the cortical record the obvious spike pattern could be localized to a discrete area; however, we could see some evidence of spread of this discharge to other areas. We knew that the hemisphere probably had rather widespread damage; hence hemispherectomy was carried out.

DR. VILTER: Dr. McLaurin will now tell us about the operation.

DR. ROBERT L. MC LAURIN: Actually there is not much to tell. I think we can depict the result with lantern slides. What was done was simply a complete removal of the right hemisphere. This hemisphere was generally quite atrophic, with small, irregular gyri. This was true of the entire hemisphere, but atrophy was maximal in the parietal region with cyst formation, which collapsed when cerebrospinal fluid was evacuated from the lumbar space. The plane of removal of the right hemisphere was along the internal capsule, with preservation of the caudate nucleus and thalamus. The plan was to extirpate the lenticular nucleus with the hemisphere. I want to show a picture of the empty right side of the skull after removal of the hemisphere. In the center is the residual stump of the right hemisphere and the mesial face of the left hemisphere on the other side.

DR. J. PAUL WOZENCRAFT: What is the mortality in this procedure, Dr. McLaurin?

DR. MC LAURIN: It should be quite low. Perhaps Dr. Aring can answer better than I because he is more familiar with the recent literature. My guess would be that it should not be over 10 per cent.

DR. ARING: I think a bit lower than that, don't you Dr. Greenfield?

DR. J. G. GREENFIELD: Much lower than that.

DR. VILTER: Dr. McLaurin, would you tell us about the postoperative course?

DR. MC LAURIN: This patient died on March 3, a month after surgery. After the operation he would talk at times; sometimes he would swear volubly. He took nourishment if urged to do so, but had to be maintained largely by tube feedings. Catheter drainage of the bladder was instituted. Usually he had to be shaken to be aroused; he seemed rather continuously drowsy. He would open his eyes, look about, moan incoherently, and go back to sleep. He moved all of his extremities (the right more than the left), sometimes with considerable vigor when kicking at the side-rails of the bed.

Postoperatively he had little or no seizure activity. On February 4 slight tonicity and generalized muscular twitching were observed during his bath. Thereafter, rare twitching movements were noted in the right limbs and right side of the face.

He was got up in a chair beginning February 10. He vomited tube feedings with increasing frequency beginning in mid-February. He gradually became even less responive. From February 7 to 12 his intracranial pressure was measured at around 250 mm. of water in daily lumbar punctures; the cerebrospinal fluid was xanthochromic. After February 13 the cerebrospinal fluid pressure was normal, although it arose to 240 mm. on the day of death. The fluid was faintly xanthochromic.

Cn February 28 his temperature arose to 105.8° F. and on March 1 rales were heard in both lungs. There was mild cyanosis and labored respiration and he was completely unresponsive. He died on March 3, 32 days after the hemispherectomy.

PATHOLOGIC DISCUSSION

DR. JOSEPH SMITH: We have come some way since Dr. Roberts Bartholow made his historic experiment in this city about 80 years ago. You will remember that he was the first to stimulate the cortex electrically in a human with the production of contralateral movements and convulsions.

In relating the findings in the present case, I will describe first the removed hemisphere. It was considerably shrunken and in two main portions; these placed together measured 15 by 10 by 3 cm. after fixation. On the lateral surface all the gyri appeared to be narrowed but they were in apposition; medially, the right half of the corpus callosum and part of the ependyma lining the ventricular system, as well as the surface of gyri and a ragged plane of cleavage through the basal ganglia, were identified.

Coronal sections showed extensive patchy, gray discoloration of the white matter, with some cystic areas and rather less damage to the cortex. I have not time for detailed analy-

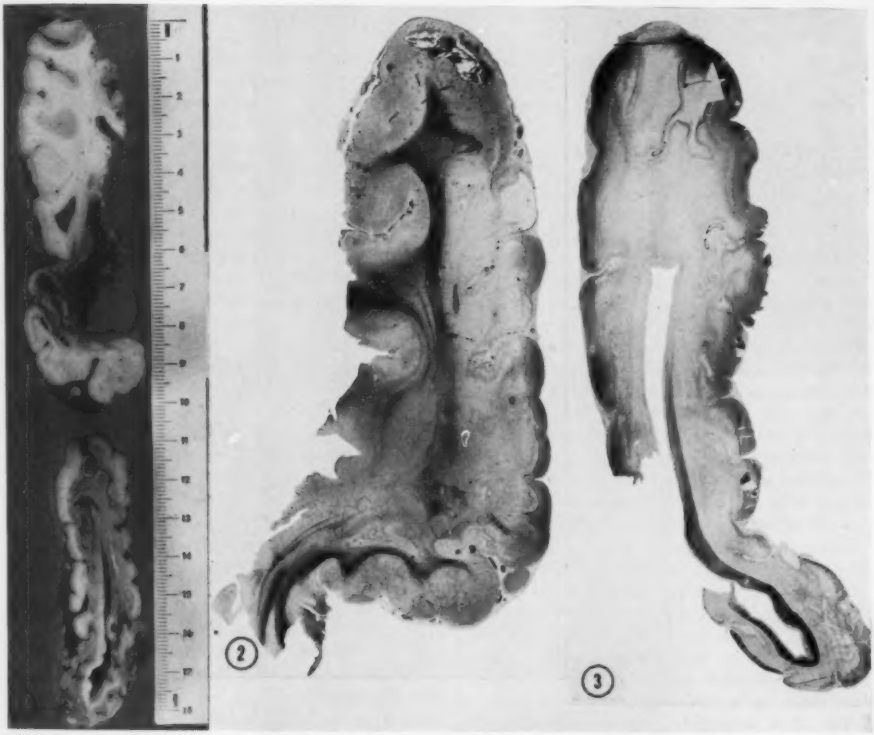

FIG. 1. Coronal sections through levels of anterior temporal lobe (above) and vestibule (below) of removed right hemisphere, viewed from in front.
FIG. 2. Section of removed hemisphere at level of anterior frontal lobe, from behind. Klüver's stain.
FIG. 3. Section of removed hemisphere at level of anterior vestibule. Note preservation of myelin in optic radiation. Klüver's stain.

sis, but the photograph of coronal sections at the level of the anterior temporal lobe (above) and the vestibule (below) (figure 1) together with myelin sheath stains of large sections through the anterior frontal lobe (figure 2), the vestibule (figure 3), and the occipital lobe (figure 4) enable me to make the main points. The section through the anterior temporal lobe illustrates cystic encephalomalacia of the superior gyrus and less severe damage of the middle and the inferior gyri, while the precentral gyrus and adjacent frontal lobe are relatively normal except for operative hemorrhage. That through the hind end of the vestibule shows extensive damage to almost the whole of the white matter, except a zone lateral to the lower part of the ventricle, and lesser damage to gray matter. The marked dilatation of the ventricular system present in the roentgenograms is not so evident now, presumably because of the aspiration of fluid at the time of operation, with consequent shrinkage.

In figure 2, which is just anterior to the genu of the corpus callosum, it is interesting to note that the residual myelin fibers adjacent to the medial and upper gyri of the frontal lobe are those of Flechsig's zones 15 and 15a; the lateral destroyed ones correspond to 28 and 35. In figure 3 at the anterior end of the vestibule the optic radiation is the only well-myelinated area, the adjacent parietal (Flechsig's 16, 33, and 34) and temporal cortex (Flechsig's 23, 36 and 26) showing only a few fibers. Figure 4 through the anterior end of the calcarine fissure illustrates the presence of myelin sheaths in the cores of gyri on the medial and inferior part of the occipi-

tal lobe (Flechsig's 4 and 17) and their absence superiorly and laterally (Flechsig's 22 and 24).

Although there were a few exceptions, this pattern of preservation of myelin in fibers that are myelinated at or soon after birth and its absence in fibers that are myelinated late was maintained. In some of the non-myelinated areas axis cylinders were also absent and the whole of the tissue replaced by a loose glial network with rather small astrocytes and scanty fibrils. In the gray matter the microscope confirmed that damage was less extensive than in the white, but it was variable. In some places, such as the superior part of the occipital lobe, there was complete necrosis; in others, such as the temporal lobe (figure 3), a patchy destruction occurred and in others, such as, the superior parietal lobe (figure 3), only a focal loss of neurons was seen. In the damaged areas astrocytes and glial fibrils were present. No evidence of a recent reaction was present in any area and no vascular lesion of any sort was identified.

In summary, this removed right hemisphere showed extensive patchy damage to gray and white matter, more particularly to the latter. The damaged areas were not restricted to the particular zone of any artery or group of veins. There was some indication that those fibers which myelinated late were more affected than those in which myelination is present at birth. This would be in keeping with the clinical indication that the damage to the nervous system started some time after birth.

Now turning to the postmortem examination, I may as well say that this indicated clearly that the cause of death was a severe bilateral lobular pneumonia, the only other findings of note outside the nervous system being a slight cardiac enlargement (360 gm.), acute and chronic splenitis, renal tubular degeneration, mild pyelonephritis, and a terminal centrilobular zonal necrosis in the liver. However, I was unable to explain clearly why the patient's conscious state was so impaired in the 32 days between operation and death. At necropsy there were 300 cc. of fluid in the subdural space on the right side and, although slight left cingulate herniation was noted, there was no gross shift of the left hemisphere to the right. The remaining brain at the time of death weighed 900 gm. There was no abnormality in the venous sinuses or in the arteries at the base of the brain. The external surface of the left hemisphere was normal and coronal sections of this hemisphere (figure 5 and 6) showed no gross abnormality except a small focus of recent softening in the white matter of the left frontal lobe. Microscopically, the recent nature of this was confirmed and it was related to a small branch of the left anterior cerebral artery that had been clipped at operation. Older damage in this hemisphere was confined to patchy and slight loss of cortical neurones such as might occur in a person with repeated convulsions. It is interesting to compare dimensions of the two hemispheres at any given level (figure 6).

Turning to the brainstem, we see that the thalamus on the right side was considerably reduced in size compared to that on the left; microscopically this shrinkage was associated with neuronal loss and astrocytic proliferation. Rather more of the right lenticular nucleus had been left than anticipated and here adjacent to the plane of cleavage there was, of course, moderate foam cell reaction, endothelial proliferation, and small vessel occlusion. A few foci of similar recent damage were present in the shrunken thalamus adjacent to the third ventricle. However, the degree of damage in these structures did not impress me as in any way unusual and there was no midbrain or pontine hemorrhage or necrosis. I had rather expected to find some in view of the postoperative course. This is the only example of hemispherectomy for infantile hemiplegia in which it has been my privilege to examine both the operative specimen and the brain a few weeks later and there are very few recorded cases in the literature with which to compare the present findings. Bearing in mind these limitations, I would suggest that the damage in the residual right lenticular nucleus is the usual inevitable accompaniment of operation (if the lenticular nucleus is left in situ) and that the focal softening in the thalamus, while not inevitable, might often occur with the operation. No changes were demonstrated in the left basal ganglia, left thalamus, cerebellum, or medulla.

CLINICAL DIAGNOSIS

Infantile cerebral hemiplegia with atrophy involving the right cerebral hemisphere.

DR. ARING'S DIAGNOSIS

Infantile cerebral hemiplegia with atrophy involving the right cerebral hemisphere.

PATHOLOGIC DIAGNOSIS

Sequel to hemispherectomy for diffuse encephalomalacia of right cerebrum. Focal encephalomalacia (operative) of right basal ganglia and thalamus. Bilateral lobular pneu-

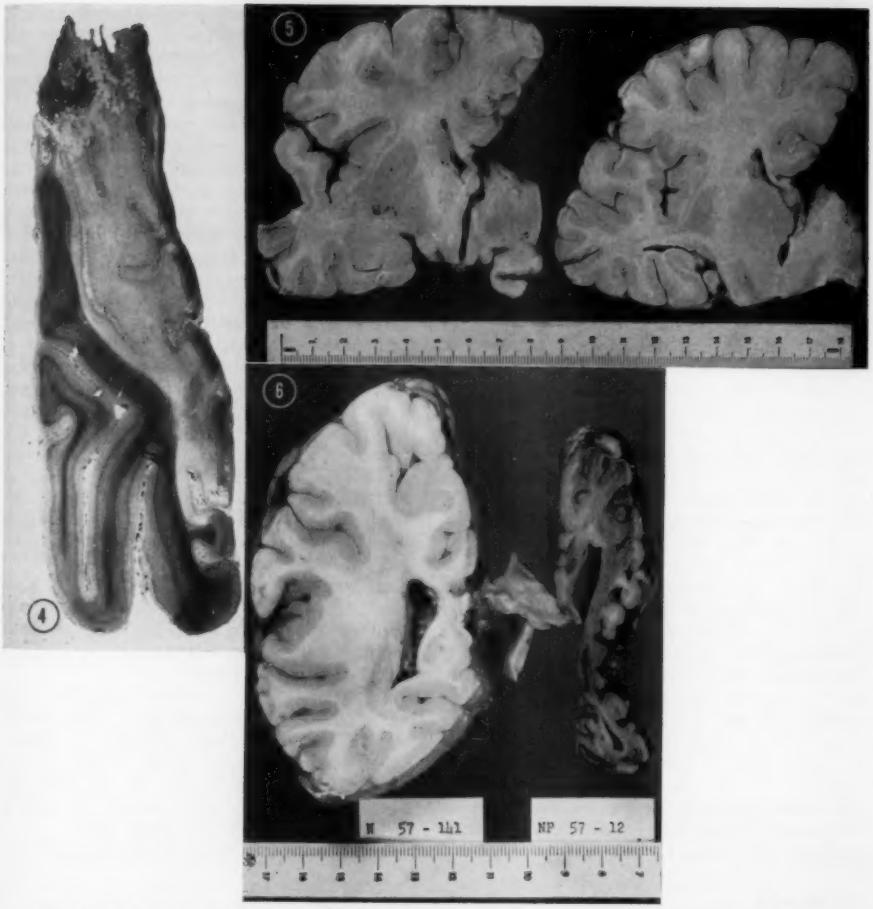

FIG. 4. Section of removed hemisphere at level of anterior end of calcarine fissure, from behind. Klüver's stain.

FIG. 5. Coronal sections of residual brain. No significant damage to left hemisphere, slight encephalomalacia in right basal ganglia adjacent to plane of cleavage, from behind.

FIG. 6. Coronal sections of residual brain and operative specimen from behind at level of vestibule.

monia. Slight cardiac hypertrophy. Focal pyelonephritis. Centrilobular zonal necrosis of liver.

DR. GREENFIELD: We have had at Queen Square quite a considerable series of these cases which are not yet published, except for a preliminary note on about 25 which was published in lecture form.[3] We hope that more is coming out very shortly, particularly in relation to the pathology. In this series which was published, there were three main types of lesions which Dr. Aring has mentioned. First of all the Sturge-Weber type with facial nevus and nevoid enlargement of vessels on one side. There you definitely have a hemispheral lesion affecting only one hemisphere and a very suitable type for this operation. The second type consists of the cases with a large cyst, usually in the central part of the hemisphere between the frontal and occipital poles, with little involvement of the temporal pole. This appears to be a birth injury and is often associated with

a residual lesion in the middle cerebral artery in the sense of a small intimal swelling, which may be, and is thought by pathologists to be, the remains of an embolus. It has been suggested that this might come from the umbilical vein at birth. These cases have had no severe difficulty in birth, but very often have shown symptoms such as difficulty of breathing at birth.

The third series of cases are of the type with which we are dealing today. In these a normal baby goes on well for a year or 18 months, sometimes considerably more, and then has a series of seizures, sometimes after an illness, sometimes without any illness to bring them on, and after that is hemiplegic. You may have the same sort of thing followed by idiocy when there is a more diffuse type of lesion, and those cases are also well known.

The cases in which there is hemiplegia are not easily explained. One can only go on one's own experience of what one has found in certain cases which have died immediately after or soon after that sort of thing has happened. In them we have had three types of lesions. These are cases of vascular thromboses on either the arterial or venous side. These may be blockage of a single vessel, either the anterior or middle cerebral, which causes the hemiplegia. Of course in the case of the anterior cerebral artery, the hemiplegia is mostly in the leg. In the second type of case, of which I've seen one or two, the brain shows areas of infarction of the cortex which may be very extensive but elsewhere the cortex is normal. In those cases there is no evidence of any inflammation at all and we do not know the cause of these infarctions. They are often multiple; they may be bilateral or unilateral. The third type of case is the definitely encephalitic, but it is difficult to conceive of encephalitis attacking one hemisphere alone. I have no evidence of that in my own experience and it is difficult to imagine.

There is one other point which perhaps one might mention here as perhaps a help in arriving at a diagnosis as to the etiology of this case. In general, a lesion of the arteries tends to damage the cortex rather locally and more than the white matter. The white matter under the cortex, of course, is damaged, but as a rule there is no damage of white matter under intact cortex; whereas in venous lesions there may be damage to the white matter with comparatively little damage to the cortex or partial damage to the cortex in the sense that certain cells or layers of cells may disappear, as has happened in this case. I think that, from that point of view, this case does suggest a lesion of the veins, possibly of the large vein which runs down into the transverse sinus as well as of some of the veins running up toward the vertex. However, at this interval of years it is quite impossible to say whether that was the cause or not.

DR. JOHN B. S. CAMPBELL: There has been some disagreement about how much of the basal ganglia should be extirpated; I believe Dr. Joseph P. Evans felt that the basal ganglion should not be taken.

DR. MC LAURIN: I believe Krynauw and others who have performed the majority of the hemispherectomies for infantile hemiplegia have felt that removal of the lentiform complex with dissection along the internal capsule was advisable. The caudate nucleus is spared. Am I correct, Dr. Greenfield?

DR. GREENFIELD: This has been usual, yes.

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Neurology

BOOK REVIEWS

Subarachnoid Haemorrhage

John N. Walton, M.D., M.R.C.P. 1956. Baltimore: Williams and Wilkins Company. 300 pages. $7.00.

ALTHOUGH THE author of this monograph treats his subject in the broad manner indicated by its title, it is to all intents and purposes a treatise on intracranial aneurysm, with rather incidental attention given to the angiomas and even less to rarer sources of spontaneous subarachnoid bleeding. This is only to be expected and it can be said that, from the clinical standpoint particularly, it is an excellent and exceedingly well balanced work upon the perennially challenging subject of intracranial aneurysm. Semiology, diagnosis including radiographic and other diagnostic investigations, prognosis, pathology, and treatment are all well covered. The data on which the observations are based are derived from the author's own series of 312 cases from the Royal Victoria Infirmary, Newcastle upon Tyne, and from a well considered analysis of the greater part of the literature on the subject, including all other large series reported in recent years. A wealth of detail is presented, so well organized that the book will serve as a convenient and accurate reference source as well as a guide to the management of such cases.

Two features give the book special significances in its field, namely that it is one of the few and the only thorough contemporary work or its kind written by a neurologist rather than a surgeon, and that the author's own large series of cases come from a period (1940-1949) when angiography and surgical treatment were rarely employed. A well documented control material of this size has been much needed as a check against the frequently discordant observations and conclusions of the surgeons and should go a long way toward resolving some of the problems of procedure which are still so troublesome. The author's own stand on the vexing questions of surgical versus conservative treatment, the type of operation best employed, and the timing of angiography and surgical intervention seems to be as good as can be taken in the present state of surgical and diagnostic technics. It is gratifying, too, that the author has so effectively made the point that the "conservative" treatment of intracranial aneurysm is actually a rational course of action under some circumstances and not merely a euphemism for helpless inaction, as has sometimes been thoughtlessly stated.

R. B. R.

Peripheral Nerve Regeneration

A Follow-up Study of 3,656 World War II Injuries. Edited by Barnes Woodhall, M.D. and Gilbert W. Beebe, Ph.D. V. A. Medical Monograph. Available from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C. 671 pages, $3.75.

DURING THE period of World War II, there accumulated an enormous amount of clinical material in the records of the Armed Forces. At the conclusion of the war, through the cooperation of the National Academy of Sciences, the Veterans Administration, and with the support of the Surgeons General of the Army, Navy, and U. S. Public Health Service, a follow-up agency was established under the Committee on Veterans Medical Problems to initiate and nurture a general program of longitudinal studies of medical conditions. This volume records the follow-up studies on peripheral nerve injuries of five teams working in Chicago, Boston, New York, Philadelphia, and San Francisco and a sixth team working on early peripheral nerve injuries from the Korean War at Valley Forge.

The report gives in detail the technics followed in examination at the different centers. The methodology and interpretation of the

findings becomes of paramount importance in the evaluation of a large series studied by several centers. The results are presented in terms of sensory and motor function. One of the most definite factors influencing the return of motor function was time of neurorrhaphy. For all nerves, the final level of motor recovery was maximal for early sutures and was impaired about 1 per cent of maximal performance for each six days of delay after wounding. It is true that nerves treated by suture within 19 days often required resuturing. The gross appearance of the nerve ends correlated to some extent with the pathologist's report of their condition and with eventual motor recovery. The method of suturing—silk, tantalum wire, or plasma glue—seemed to have no influence upon the final motor status. Although nerves cuffed about the suture line with tantalum seemed to regain better motor function than those without cuffs, the difference was probably related to selection of cases. Stay sutures did not modify the amount of motor recovery.

The special examinations for electrical evidence of regeneration had value in indicating the cause of functional motor paralysis. In general, those muscles which moved voluntarily or upon intraneural stimulation were innervated, whereas those muscles not contracting were denervated. Reinnervated muscles not contracting voluntarily were more frequently found in the lower than upper extremity.

The sensory recovery was studied with particular reference to pain and touch in autonomous zones. The degree of sensory return was not related to time of suture, length of gap in the nerve, appearance of ends, suture material, stay sutures, or experience of the surgeon. The use of tantalum cuffs seemed to be associated with better sensory reinnervation. In the lower extremity only, transposition or mobilization of nerves impaired tactile recovery but not pain.

It is concluded that early suture should be done, even though this often introduces a dilemma, since 75 per cent of high velocity nerve wounds associated with total paralysis do not require a suture and achieve an end result far better than could be accomplished by neurorrhaphy. Hence the authors suggest waiting one month before exploration. Operation is not indicated if regeneration is occurring. Certain evidence of recovery is 1) voluntary motor function 2) preservation or recovery of sensation, 3) preservation of sweating, 4) motor response on nerve stimulation. Equivocal evidence is 1) advance of Tinel's sign, 2) shrinkage of area of sensory loss, 3) improvement in use of extremity, 4) electromyography, 5) chronaxie, and 6) galvanic tetanus ratio.

This monograph is an example of the value of longitudinal studies of clinical material which can be followed for years. As might have been predicted, the studies have not revealed startling discoveries, but they do confirm or dispose certain concepts which were suggested as the result of fragmentary experiences in World War I and II. The reader of this book will gain a clear appreciation of the complex nature of the problems of peripheral nerve injuries even if he does not find "black and white" answers to all questions. Neurologists, neurosurgeons, and, indeed, all physicians who care for wounds of the extremities are indebted to the authors, who have labored long in this work for this essential data. Because of the statistical nature of the material, the style is not conducive to easy reading, but it is clear and concise. Adequate references to recent litterature are appended. The indices, both to names and subjects, should be helpful.

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PNEUMOENCEPHALOGRAPHY

By

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OCTOBER 1957

History of Brain Knowledge Subject of London Symposium

The history and philosophy of knowledge of the brain and its functions was the central theme of an Anglo-American Symposium held in London (July 15-17) under the sponsorship of the Wellcome Historical Medical Library, with the cooperation of the National Hospital, Queen Square, and the Maudsley Hospital. A selected group (by invitation) of about 70 neurologists, psychiatrists, neurologic scientists, medical historians, logicians, and philosophers provided themes and discussions for the full-day sessions.... The program was organized by a London committee chaired by Macdonald Critchley,[1] with the advice of a special U. S. subcommittee which your reporter had the honor to chair.[2] Both committees are indebted for help and advice to John F. Fulton (Yale University), who regrettably had to leave London just prior to the symposium because of illness.... Originally inspired by Horace W. Magoun and Robert B. Livingston, the symposium was planned as a historic introduction to the First International Congress of Neurological Sciences, Brussels, July 21-28. (Newsletter, July 1957.)

Program Features Exhibits and Formal Presentations

Following a welcoming address by Mr. M. W. Perrin, chairman of the Wellcome Foundation, the historic exhibits prepared for the symposium were officially unveiled by the American Ambassador, Rt. Hon. John Hay Whitney, who is a son-in-law of the late Harvey Cushing.... Among the American exhibits was the monumental arbeit by Magoun and Kruger on the growth of knowledge of the brain; Tibetan and Japanese concepts of the brain and psychic function designed respectively by Ilza Veith and Gordon Mestler; and the NINDB exhibit on the personalities and topics of the First International Congress of Neurological Sciences. The British exhibits, prepared by the director of the Wellcome Medical Museum and Library, Dr. E. Ashworth Underwood, provided interesting displays on prehistoric and primitive trephination, popular phrenology, and one on Pierre de la tete (pierre de la folie); and two centenary exhibits: the first in honor of Sir Victor Horsley (1857-1916), by Sir Geoffrey Jefferson (Manchester); the second in honor of Sir Charles Scott Sherrington (1857-1952), by Prof.

[1]Other members of the London committee were Sir Russell Brain, Sir Geoffrey Jefferson, Aubrey Lewis, and F. N. L. Poynter, Secretary, who ably administered the entire program to the finest detail.
[2]On the U. S. subcommittee were Mary A. B. Brazier, Webb Haymaker, Robert B. Livingston, Horace W. Magoun, and James L. O'Leary.

E.G.T. Liddell (Oxford). Also, there was a centenary exhibit in honor of J.F.F. Babinski (1857-1932) structured from memorabilia procured through the courtesy of Prof. Auguste Tournay (Paris) and forwarded to London by Dr. Robert A. Esser of the U. S. Public Health Service at the American Embassy in Paris.

Scientific Sessions Opened by Wilder Penfield The first formal papers were presented in the Wellcome Auditorium (July 15) under the chairmanship of Wilder Penfield. Included were concepts of the brain in classic antiquity by D. H. M. Woollam (Cambridge); body and soul in the Aristotelian tradition by J. S. Wilkie (London); and non-Western concepts of psychic functions by Ilza Veith (Chicago).... The next morning (July 16) the program opened at the National Hospital, Queen Square, under the chairmanship of Pearce Bailey, with presentations on the origins of language by Macdonald Critchley (London); old and new concepts of the basis of consciousness by Denis Williams (London); and Hughlings Jackson's ideas of consciousness by Sir Russell Brain (London). The same afternoon J. Eccles (Canberra) presided in sessions which included medieval and renaissance contributions by Walter Pagel (London); Cartesian concepts by Walther Riese (Richmond); and ideas on neural action from Willis and Newton to Hume and Bichat by W. P. D. Wightman (Aberdeen).... The Wednesday morning sessions (July 17) were conducted under the chairmanship of Bernard Hart (London) at the Maudsley Hospital, where papers were read on the contributions of the phrenologists by E. H. Ackerknecht (Zurich); on Reil's concepts of brain function by Aubrey Lewis (London); on emotions and the pituitary in the 19th century by G. W. Harris (London); and on chemical contributions from the 19th century on by H. McIlwain (London). The concluding sessions on Wednesday afternoon were held in the Wellcome auditorium and chaired by Sir Wilfrid Le Gros Clark (Oxford). Mary Brazier spoke on the history of electrical activity, Sir Francis Walshe (London) on the opening phase of the physiology of the cerebral cortex, and Chandler Brooks on the origin of ideas of integrative function.

Official Reception In traditional London hospitality, a series of receptions and luncheons were offered to the conferees. On Monday evening (July 15), a reception and buffet was given by the Wellcome Foundation, followed on the next evening by a sherry party at the Royal College of Physicians, given by the president and fellows. The concluding social ceremonies on Wednesday evening (July 17) consisted of a subscription dinner at the historic Apothecaries' Hall. Here a toast was proposed by Sir Henry Dale and replied to by Pearce Bailey. The festivity ended with a brief talk on the history of Apothecaries' Hall by Macdonald Critchley, Master of the Worshipful Society of Apothecaries.

Neurology Banquet Held in Antwerp

Saturday evening (July 27), at the close of the First International Congress of Neurological Sciences in Brussels, the publishers of NEUROLOGY, sponsored a banquet for American Academy of Neurology members attending the Congress, AAN honorary-corresponding members from other lands, and distinguished guests. The entire task of organizing the banquet was graciously assumed by the Secretary-General, Ludo van Bogaert, who quickly perceived the need for something ultra special. With this thought and with a desire to celebrate the occasion in a finely preserved patrician structure of the Flemish renaissance, he procured for the banquet the grand salons of an historic private estate in Antwerp, called Hotel Osterrieth, now owned and maintained by the Paris and Netherlands Bank and used for extraordinary functions only. This elegant decor, coupled with the friendliness of the reception, created an atmosphere of warmth and dignity in which the 105 guests of the publishers of NEUROLOGY intermingled harmoniously; the group comprised 23 honorary-corresponding members,[3] 10 distinguished guests, and as many AAN members and their wives, as could be reached in Brussels. Centered at the head table was Mr. Jay H. Herz, co-publisher of NEUROLOGY, flanked by the American Consulate General and Mrs. Prescott Childs, Dr. and Madame L. van Bogaert, Prof. F. Bremer, Drs. J. Rademaker, J. Titeca, and your reporter. After a five-course gourmet dinner accompanied by four different grand vintage wines, there followed a series of spirited toasts to individuals present and to the thesis of greater international collaboration in neurology. President Forster then spoke on behalf of the Academy; Dr. van Bogaert expressed, warmly, in French, the real appreciation felt by the honorary-corresponding members and their wives, as did also Prof. G. H. Monrad-Krohn (Oslo) in his customary witty, anecdotal and graceful English. Just prior to adjournment, Dr. J. Chandy of India arose and expressed forcefully the value of the AAN as an integrating force toward international collaboration.... Chartered busses brought the banquet guests from Brussels to the Osterrieth and return, providing en route a quick sight-seeing tour of the port and the ancient part of the city of Antwerp.

World Federation of Neurology Organized in Brussels

Before the Brussels Congress, Secretary-General van Bogaert invited the official delegates to the Sixth International Neurological Congress to convene for the purpose of considering the formation of a World Federation of Neurology. As a result of two meetings (July 22 and July 26), both held at the Fondation Universitaire, Brussels, the delegates

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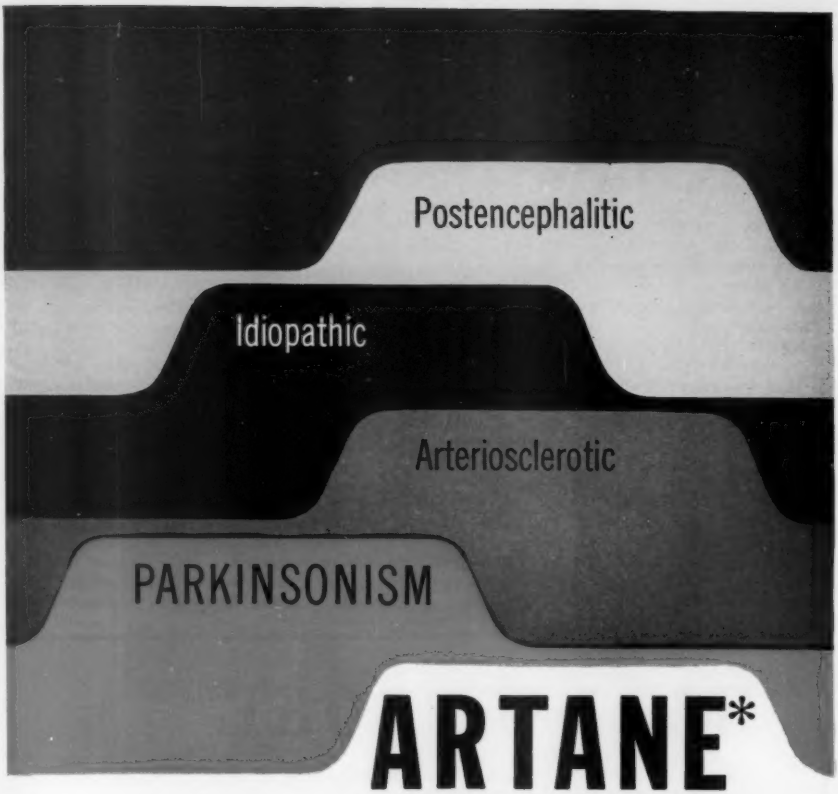
[3]The honorary-corresponding members present were: I. S. Aksel (Constantinople); F. Bremer (Brussels), V. M. Buscaino (Naples), J. Chandy (Calcutta); Macdonald Critchley (London), E. Frauchiger (Zurich), R. Garcin (Paris), K. Henner (Prague), K. Krabbe (Copenhagen), T. de Lehoczy (Budapest), A. Lima (Lisbon), F. Lüthy (Zurich), G. H. Monrad-Krohn (Oslo), S. Okinaka (Tokyo), J. Pereyra-Kafer (Buenos Aires), C. M. de Rojas (Havana), S. Refsum (Oslo), G. Schaltenbrand (Wurzburg), A. Subirana (Barcelona), E. Tchehrazi (Teheran), O. Trelles (Lima), L. van Bogaert (Antwerp), and K. Winther (Hellerup, Denmark).

from 29 nations, first, unanimously approved the van Bogaert proposal, then voted themselves as constituting a provisional executive committee of the federation and appointed a committee to draft a provisional constitution. This committee was composed of H. Houston Merritt and Pearce Bailey (U.S.A.), Macdonald Critchley (United Kingdom), G. Schaltenbrand (Germany), Auguste Tournay (France), and Ludo van Bogaert (Belgium). Finally, a provisional constitution was adopted and a slate of officers elected: president, Ludo van Bogaert (Belgium); vice-presidents, Auguste Tournay (France) and Macdonald Critchley (United Kingdom); secretary-general, Pearce Bailey (U.S.A.). Prof. G. Schaltenbrand (Germany) was named chairman of a committee on constitution and by-laws.... The principal objective of the federation is to serve as a formal representative body for the advancement of neurology throughout the world, for the organization of international neurologic congresses and symposia, and serve as a liaison body with federations of allied disciplines for combined international congresses of neurologic sciences.... Copies of the provisional constitution have been forwarded for confirmation to the national neurologic societies of the countries represented by the delegates, or their alternates, in Brussels.

Next International Neurological Congress To Be Held in Rome

The Seventh International Neurological Congress is tentatively scheduled to be held in Rome the third week in September 1961. The Fourth International Congress of Neuropathology will be held in Munich the second week in September 1961. Tentatively, the Sixth International Congress of Electroencephalography and Clinical Neurophysiology is scheduled for either the week preceding or following the third week in September 1961. Joint sessions for these three congresses are under consideration. The Second International Congress of Neurological Surgery will be held the same year, possibly in Washington, D. C.... It is believed by many that a second international congress of neurological sciences would be apropos in 1965, probably in the U.S.A.

Pearce Bailey



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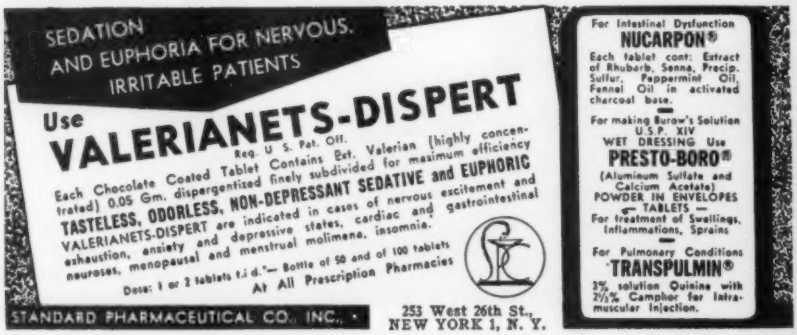
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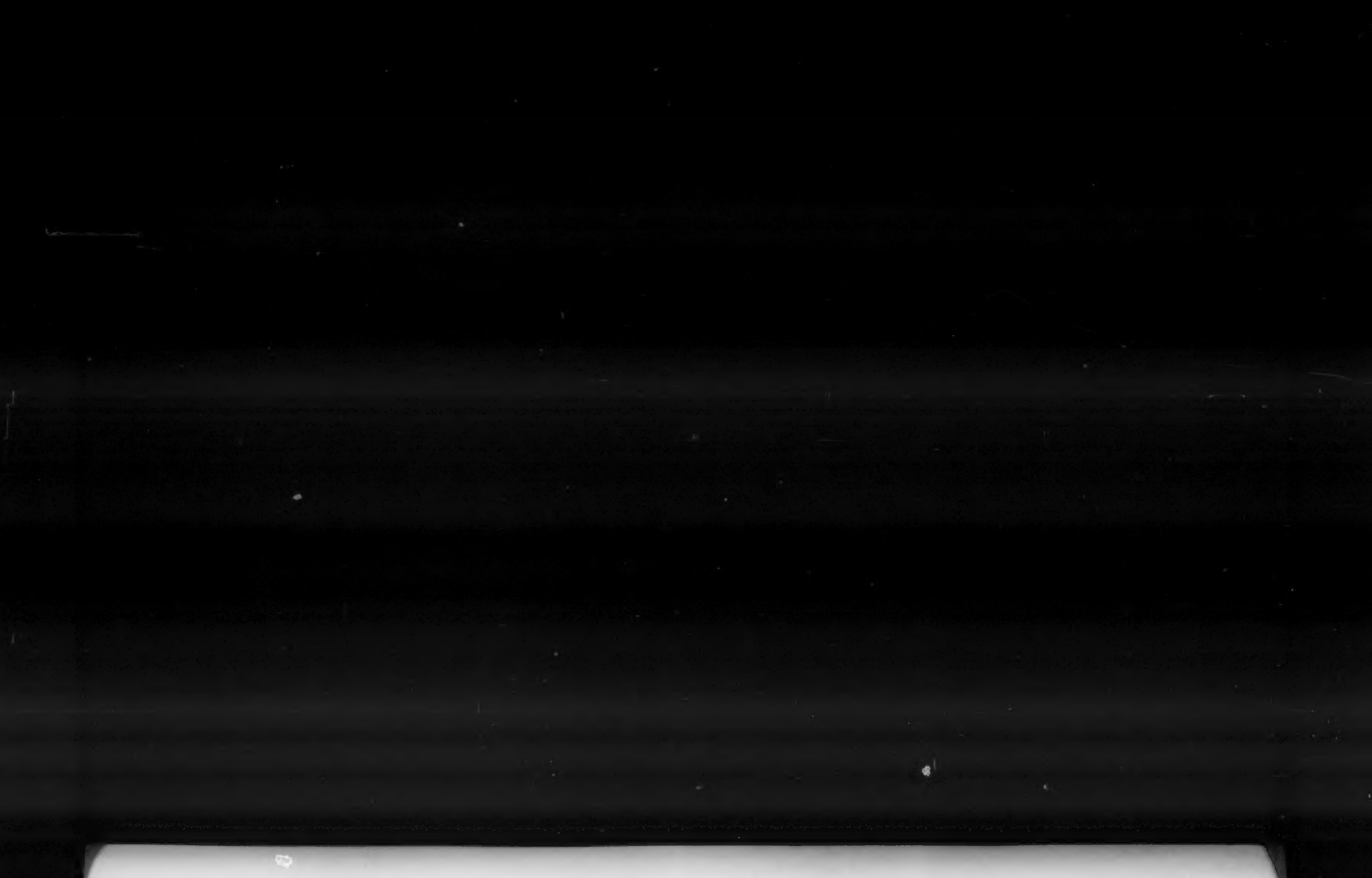
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